

IOXAGLATE

AN IONIC DIMERIC RATIO 3.0

CONTRAST MEDIUM

**Effects following intravascular injection in animal and man
with special reference to haemodynamic and subjective
responses, tolerance, and image quality**

PAUL E NILSSON



1985

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To

Gunilla

Kamilla

Jacquelin

Raoul Lukas

Paul Ludvig

I was introduced to research on contrast media because I was on the wrong place, at the wrong time and especially because I could not keep my big mouth shut.

" Honi soit qui mal y pense " * as
King Edvard III of England said in 1350
when the countess of Salisbury lost her garter.

* = " Vanärad den, som tycker illa därom ",
ordspråk för Strumpebandsorden (Knights of Garter).

This thesis is based on the following papers:

- I. ALMÉN T, ASPELIN P and NILSSON P: AORTIC AND PULMONARY ARTERIAL PRESSURE AFTER INJECTION OF CONTRAST MEDIA INTO THE RIGHT ATRIUM OF THE RABBIT.
Comparison between metrizoate, ioxaglate and iothexol.
Acta Radiol Suppl 362 (1980) 37-41
- II. NILSSON PE, HOLTÅS S and TEJLER L: SUBJECTIVE RESPONSES AND ALBUMINURIA INDUCED BY IOXAGLATE DURING RENAL ANGIOGRAPHY IN MAN.
Radiology 144 (1982) 509-512
- III. NILSSON PE, ASPELIN P, NYMAN U and HEDNER U: TOLERANCE AND BIOCHEMICAL EFFECTS FROM INTRAVENOUS INJECTION OF IOXAGLATE IN HEALTHY VOLUNTEERS.
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- IV. NILSSON PE and JONSSON K: EFFECT OF IOXAGLATE ON THE LIVER AND PANCREAS FOLLOWING SELECTIVE VISCERAL ANGIOGRAPHY IN MAN.
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- V. NILSSON PE, ASPELIN P and HOLTÅS S: DEMONSTRATION OF THE RENAL VENOUS SYSTEM AT ROUTINE RENAL ARTERIOGRAPHY.
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- VI. NILSSON PE, ASPELIN P and ELMQUIST D: AORTOCERVICAL ANGIOGRAPHY WITH HIGH AND LOW IONIC OSMOLALITY CONTRAST MEDIA.
A clinical investigation of metrizoate and ioxaglate.
Accepted for publication in Acta Radiol Diagnosis.

These papers will be referred to in the text by their Roman numerals, I - VI.

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INTRODUCTION and HISTORICAL REMARKS

The radioopacity of vessels and various organs to X-rays can be increased with support of different contrast media. In January 1896, only a few weeks after Wilhelm Conrad Röntgen announced his discovery of the X-ray, Hascheck and Lindenthal injected a thick emulsion of chalk as contrast medium into the vessels of an amputated hand. Between 1896 and 1923 several investigations were performed in animals and cadaver preparations mostly with solutions and/or suspensions of heavy metals and oils. The intravascular use of these contrast media caused intolerable systemic toxicity or embolism.

In order to achieve high intravascular radioopacity it was necessary to synthesize contrast media, which allowed rapid injections of highly concentrated water solutions. Therefore it became important to combine in one molecule low toxicity, high water solubility, high attenuation of X-rays (high iodine content) and low viscosity. As some side effects of contrast media (e.g. pain in arteriography) were caused by the high osmolality of highly concentrated solutions it also became important to reduce the osmotic effects of contrast media.

The ideal intravascular contrast medium should have the following properties:

1. high attenuation to X-rays,
2. low toxicity, which includes low osmolality,
3. high water solubility,
4. chemical stability to tolerate autoclaving and long storing,
5. low viscosity (in some cases)
6. selective excretion (e.g. high renal excretion for urography, high biliary excretion for cholangiography),
7. low price

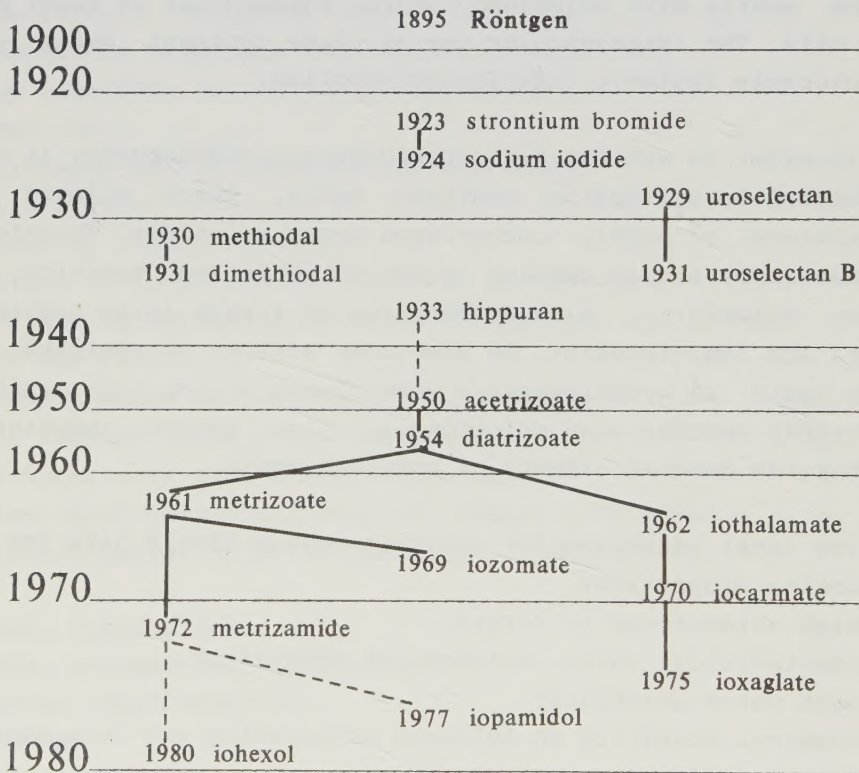
The radioopacity relative to the osmolality of a contrast medium solution is described by its Ratio = the number of iodine atoms / number of particles in an ideal solution.



The clinical development of INTRAVASCULAR WATER-SOLUBLE CONTRAST MEDIA (Fig 1) from the early 1920's have in principle been achieved by synthesizing inorganic compounds, organic sulfonates and cyclic organic compounds (1,2,3,4).

Fig 1.

Evolution of water-soluble contrast media



In 1923 (5) sodium iodide (ratio 0.5) was introduced as a contrast medium. Sodium iodide proved far too toxic for routine radiodiagnostic purpose and it induced extreme pain during arteriography, probably due to the high osmolality, and these patients required general anesthesia (6,7). Iodine however became the atom of choice to obtain radioopacity because it exhibits

high absorption of X-rays and can be incorporated into chemically stable molecules. In order to reduce the toxicity of the contrast medium the iodine atom was incorporated into organic substances. Table 1 gives the relation between the LD₅₀ of some of these organic compounds according to Hoppe et coll. (8).

Table 1 Acute intravenous LD₅₀ in mice
Contrast medium mg I / kg mouse

Methiodal (Abrodil)	16
Iodomethamate (Uroselectan B)	18
Iodopyracet (Diodon)	25
Hippuran	10
Acetrizoate (Urokon)	43
Diatrizoate (Hypaque, Urografin)	66

Ionic monomeric contrast media /ratio 0.5 – 1.0/

Such organic compounds were the mono-iodinated sulfonate methiodal (Abrodil, Fig 2) and the corresponding di-iodinated dimethiodal (Tenebryl) introduced in 1930 and 1931 respectively (9,10).

Other organic contrast media such as the mono-iodinated pyridine ring uroselectan (1929, Uroselectan, Fig 2) and the di-iodinated analogues iodomethamate (1931, Uroselectan B, Neo-Iopax) and iodopyracet (1931, Perarbrodil, Diodrast, Diodon) were synthesized (11-13).

These organic contrast media were water-soluble but the problems with low content of iodine, high toxicity and high osmolality (ratio 0.5-1.0) remained.

Early in the 1930's efforts were made to reduce the toxicity of the contrast medium by incorporating the iodine atom into a substance normally appearing in the urine of man, hippuric acid. In 1933 hippuran (Hippuran, Fig 2) was introduced (14). It was the first intravascular contrast medium that was based on a benzene ring. Hippuran (ratio 1.0) was too toxic to be an improvement compared to uroselectan or iodopyracet, as the introduction of the iodine atom increased the toxicity of hippuric acid by 100 % (Table 1).

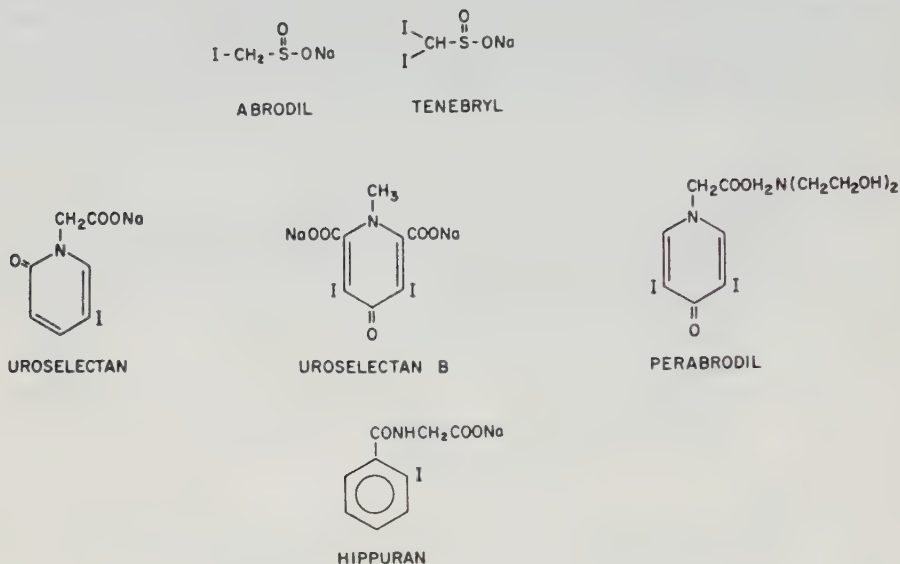


Fig. 2 Chemical formulas of Abrodil, Tenebryl, Uroselectans and Hippuran

The contemporaneous development of the angiographic procedure necessitated the use of more concentrated less toxic contrast solutions. Instead of hippuric acid its precursor benzoic acid was used.

Ionic monomeric contrast media /ratio 1.5/

The development of intravascular contrast media was forwarded with the synthesis of the the first tri-iodinated benzoic acids (Fig 3). These compounds were the result of a methodical study begun by Wallingford in 1944 (15). Acetrizate (Urokon) was introduced in 1950. Urokon was less toxic, had higher water solubility, more percent iodine per weight than previous contrast media. In 1954 More et coll. (16) and, independently, Langecker et coll. (17) introduced another acet-amido group on the 5-position and thereby further decreased the toxicity and diatrizate (Hypaque, Renografin, Urografen, Angiografin, Urovison) was synthesized. In 1961 another ionic monomeric contrast

medium metrizoate (Thiosil, Isopaque) was introduced and the year after iothalamate (Angio-Conray). An initial advantage of metrizoate and iothalamate versus diatrizoate was a more soluble sodium salt. This allowed high iodine concentration without high viscosity. The importance of this feature decreased with the introduction of other cations such as methylglucamine.

In the 1960's several of the problems were reduced to achieve the ideal contrast agent with a high opacidity to x-rays, high water solubility, good chemical stability, low viscosity and reduced toxicity. The problem with the high osmolality of the ratio 1.5 contrast agents was however not solved and there was still a need of further reduction of the chemotoxicity. The ratio 1.5 contrast media induce, when injected into the circulation, disturbances in many systems and organs in the body (18-29). Some of these effects are explained by the rather high osmolality of these contrast media relative to blood (5-7 times that of human plasma).

In the mid 1960's Hilal, Björk, Erikson, Ingelman and Almén (30,31,32) focused the research work on the high osmolality of contrast media. Lower osmolality of the contrast compound could be achieved by a.) synthesizing non-ionic monomers, b.) polymerisation of monomers or c.) synthesizing iodinated cations.

The first iodinated cation developed by Sovak et coll. in 1979 proved however to be rather toxic (33).

Table 2 (29) gives the relation between the LD_{50} of low and high osmolality contrast media.

Table 2

Acute intravenous LD50 in mice

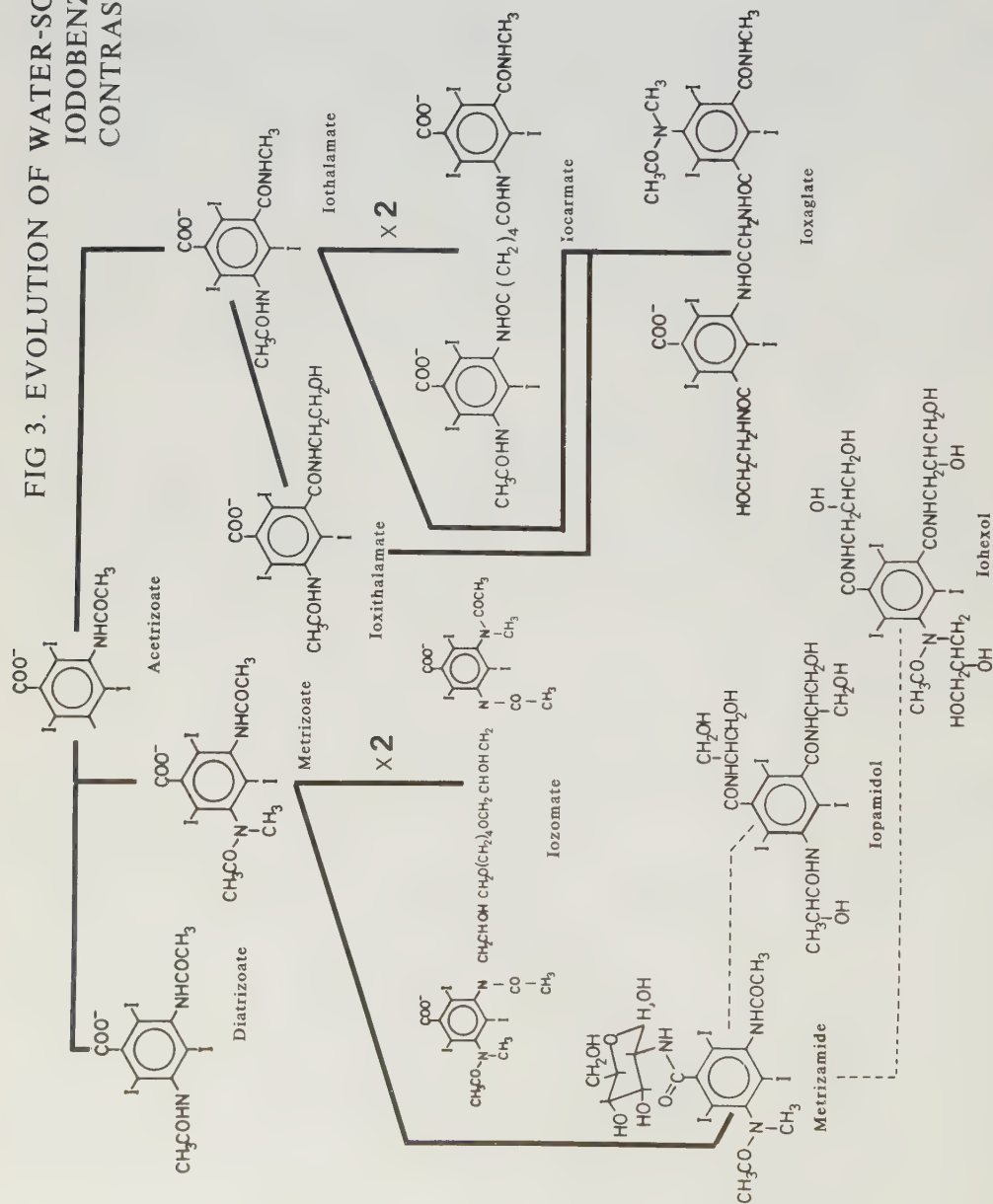
Contrast medium	gl/kg mouse
Iohexol	24.3
Metrizamide	18.1
Ioxaglate	13.5
Metrizoate	8.0

FIG 3. EVOLUTION OF WATER-SOLUBLE
IODOBENZOATE
CONTRAST MEDIA

RATIO 1.5

RATIO 2.0

RATIO 3.0



Non-ionic monomeric contrast media /ratio 3.0/

Almén (32) suggested in 1969 that the carboxylgroup of conventional contrast media should be replaced by a non-dissociating radical, which theoretically would reduce the osmolality by 50 per cent without loss of iodine content. Water solubility for the conventional monomeric contrast media had been obtained by incorporation of the carboxylgroup (acid function), from which soluble salts were prepared. In order to obtain high water solubility for the nondissociating contrast media more hydroxyl-groups were incorporated instead. The non-ionic metrizamide (Amipaque) was introduced in 1972. Metrizamide does not tolerate sterilization by autoclave, which to some extent explains why metrizamide is expensive relative to conventional monomeric contrast media. Furthermore the freeze-dried lyophilized powder has to be solved before use. There was thus need for further development of other low osmolality compounds.

Modifications of the metrizamide molecule by substituting different side chains have resulted in the next generation of low osmolality non-ionic products such as iohexol (Omnipaque) and iopamidol (Solutrast), which tolerate autoclavation (34,35).

Ionic diacidic dimeric contrast media /ratio 2.0/

Already in 1966 Hilal (30) and Hayes et coll. (36) performed experimental investigations with a dimer of iothalamate, which possessed lower osmolality than the ionic monomeric contrast media. Two iothalamate molecules were connected with a small sidechain. The dimer had still two carboxylgroups (diacidic) and the ratio of iodine atoms to number of particles in solution was $6:3 = 2.0$. The reduction of osmolality was moderate, about one third of the osmolality of the conventional ionic monomers.

The first clinical use of a diacidic dimer was published by Björk, Erikson and Ingelman in 1969 with iozomate, a dimer of metrizoate (31). The dimer of iothalamate, iocarmate (Dimer X) was introduced for routine clinical use in 1970.

Ionic monoacidic dimeric contrast media /ratio 3.0/

Ratio 3.0 contrast media can also be achieved by development of dimeric ionic contrast media. The monoacidic, dimeric and ratio 3.0 ioxaglate (Hexabrix) was synthesized in 1975 (37). Ioxaglate is a dimer of ioxithalamate and iothalamate linked by a small sidechain. The carboxyl group on one of the benzene rings is converted into a nondissociating radical. The other carboxyl group remains as meglumine and sodium salts. Ioxaglate is stable in solution and supplied ready for use. Although ioxaglate is an ionic compound it belongs to the family of low osmolality contrast media.

There are numerous reports showing that the intravascular conventional monomeric ratio 1.5 contrast media cause complex effects, when injected into the circulation, in which the high osmolality has been considered play an important role. It was therefore the

AIM of the PRESENT INVESTIGATION

to contribute to the evaluation of the intravascular usefulness of this new monoacidic dimeric ratio 3.0 contrast medium ioxaglate in radiology and whether it has any advantages compared to the conventional contrast media. The effects of ioxaglate was compared with those of other contrast media in both animal and man with special reference to haemodynamic and subjective responses, tolerance and image quality. This was performed by investigating the effect of ioxaglate on:

1. Hemodynamic response and tolerance after
 - a. renal angiography in man assessed by changes in postangiographic proteinuria (II);
 - b. intravenous bolus injection for urography in man assessed by changes in biochemical parameters, coagulation and fibrinolytic system, plasmaproteins, heart rate and blood pressure (III);

- c. selective visceral angiography in man assessed by alterations in liver and pancreatic enzymes, bilirubin, protrombin (IV);
- d. aortocervical angiography in man assessed by alterations in EEG, ECG, heart rate and blood pressure (IV);
- e. bolus injection into right atrium and ventricle in rabbits assessed by changes in pulmonary arterial and aortic systolic pressure (I).

2. Subjective responses in man during;

- a. lumbar aortography (semiselective technique) (II);
- b. intravenous bolus injection (III);
- c. aortocervical angiography (VI).

3. Image quality and diagnostic usefulness in man during;

- a. renal angiography - with discussion of influence from osmolality, viscosity, ionicity and diffusion velocity on the demonstration of the renal venous system;
- b. aortocervical angiography - with discussion of influence from osmolality, viscosity, iodine concentration, degree of involuntary movements and subjective responses on contrast density and delineation, and resulting effect on the image quality on the original key angiograms and the subtraction films (VI).

Ioxaglate was in different parts compared with;
 the monoacidic monomeric metrizoate (I,II, III,V,VI),
 the non-ionic monomeric metrizamide (II,V) and
 the non-ionic monomeric iohexol (I).

SUMMERIES of MATERIAL, METHODS and RESULTS

Details of the material, methods and results are given in paper I-VI. Fig 3 illustrates the chemical structures of the contrast media in the investigations. Pertinent data of the contrast media and solutions used in the investigations are summarized in Table 3. 100 ml of an ioxaglate solutions contains 19.65 g sodium ioxaglate, 39.30 g meglumine ioxaglate and 0.010 sodium calcium edetate.

Table 3

	IODINE CONC. mg/ml	MOLECULAR WEIGHT	SUBSTANCE CONC. mol/l	OSMOLALITY		VISCOSITY	
				mmol/kg water		mPa.s 20°C	37°C
ISOPAQUE	280	628	0.74	1460		7.2	4.0
AMIPAQUE	280	789	0.74	430		9.7	5.0
HEXABRIX	280	1258	0.37	490		8.7	4.8
OMNIPAQUE	280	821	0.74	620		8.8	4.8
HEXABRIX	320	1258	0.39	580		15.7	7.5
ISOPAQUE	370	628	0.96	2150		17.3	8.4
AMIPAQUE	370	789	0.96	550		37.0	16.0
HEXABRIX	370	1258	0.49	670		40.0	16.5
OMNIPAQUE	370	821	0.97	980		29.6	13.5

Clinical angiographic techniques

Renal, celiac, hepatic, superior and inferior mesenteric angiographies were performed percutaneously via the femoral artery according to the Seldinger technique (38). All contrast solutions were injected at room temperature by an automatic pressure injector, and with an interval between the injections of 10-15 min .

Renal angiography

The first injection was always a lumbar aortography, semi-selective technique, followed by one or several selective renal artery injections.

Semiselective renal arteriography. Thirty millilitres of contrast medium (rate 20 ml/s) was injected through a catheter with 1 end hole and 6 side holes. The tip of the catheter was

positioned in the renal artery supplying the normal kidney. With this technique 5 ml of the totally injected 30 ml is considered to reach the normal kidney (39).

Selective and high dose selective renal arteriography.

Injections of 8-15 ml (rate 4-10 ml/s) and 20-30 ml (rate 8-10 ml/s) respectively were performed through an end hole catheter with the tip placed in the renal artery.

Visceral angiography

Thirty to 50 ml contrast medium was injected into the celiac artery, 30-40 ml into the hepatic artery, 40-50 ml into the superior mesenteric artery and 15-25 ml into the inferior mesenteric artery. The injection rate was 6-20 ml/s.

Aortocervical angiography

Fifty ml contrast media (rate 30 ml/s) was injected through a pig tail catheter with 12 side holes positioned into the aortic arch about 8 cm above the aortic valves just proximal to the origin of the great vessels and remained there during the whole investigation.

Assessment of subjective response The patient was questioned about presence or absence of heat and pain. The degree of heat and pain were assessed by the patient on a 100 mm visual analogue scale (40). On this scale the left end of the line signified no heat or pain and the right end unbearable heat or pain (Fig. 4). One scale for heat and one for pain were used for all injections.

Fig. 4



Visual Analogue Scale (VAS)

Assessment of blood and urinary samples

Analyses of

biochemical parameters in blood and urin (paper II, III and IV), plasma proteins and haemostasis (paper III) were performed at the Departments of Clinical Chemistry and Coagulation Disorders, Malmö Allmänna Sjukhus, according to procedure described previously (41-52).

Statistics

Statistical significances were evaluated with

the Wilcoxon signed rank test for paired differences (I,II,III, IV,VI), Mann-Whitney rank sum test (II), the X^2 (V), Fisher exact test (V,VI) and Sign test (paper VI). P-values less than 0.05 were considered to be significant.

AORTIC and PULMONARY ARTERIAL PRESSURE after injection of CONTRAST MEDIA into the RIGHT ATRIUM of the RABBIT /I/

Material and methods

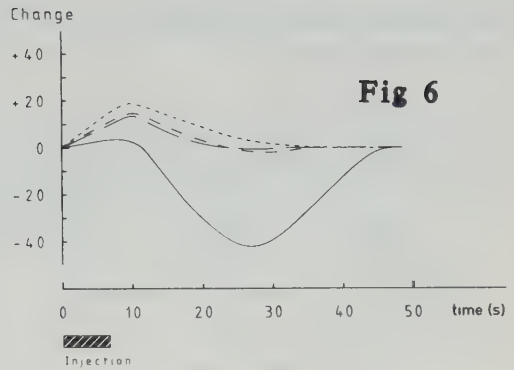
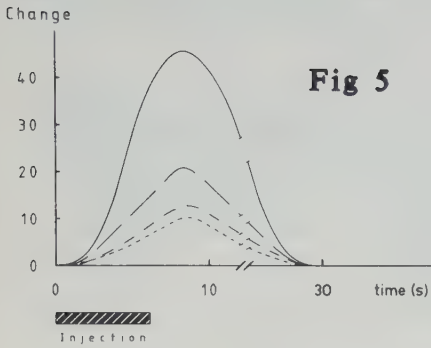
Metrizoate, ioxaglate and iohexol

(370 mg I/ ml), were injected into the right atrium of the heart in 12 rabbits (3 ml/kg BW). All rabbits received one injection of all 3 contrast media in random order with an interval of 15 min between the injections. In 5 of the rabbits an additional injection of physiologic saline was given. Pulmonary arterial and aortic systolic pressure were continuously recorded. The maximum increase or decrease in pulmonary arterial or aortic systolic pressure was expressed in per cent of the highest or lowest pressure obtained before injection.

Results

All injected solutions increased the pulmonary

arterial pressure (Fig. 5). Iohexol and ioxaglate caused significantly less increase than metrizoate. The early systolic aortic pressure (the first 12 s) was increased significantly less and the the late systolic aortic pressure (15-25 s after the start of injection) was decreased significantly more after metrizoate than iohexol and ioxaglate (Fig 6). No differences existed between iohexol and ioxaglate and the pressure changes produced were similar to those produced by saline.



Changes (%) in pulmonary arterial systolic pressure (Fig.5) and in aortic systolic pressure (Fig.6) following injection of contrast medium into the right atrium of rabbits
Metrizoate (—), ioxaglate (---), iohexol (---), physiologic saline (---)

SUBJECTIVE RESPONSES and ALBUMINURIA induced by IOXAGLATE during RENAL ANGIOGRAPHY in MAN /II/

Material and methods Changes in urinary albumin concentration following routine renal angiography were studied in 19 patients. The median total amount of ioxaglate (280 mg I/ml) was 155 ml (range 75-300 ml) and the median total amount given selectively to both kidneys was 38 ml (range 20-99 ml). The concentration of creatinine and albumin was determined in all samples. The urine albumin concentration was expressed per gram of urinary creatinine, thereby relating albumin excretion to the glomerular filtration rate.

Subjective responses following metrizoate (280 mg I/ml) and ioxaglate were compared using a visual analogue scale in 34 patients.

Results Ioxaglate did not cause significant changes in urinary albumin concentration. For comparison, the figures from an earlier investigation with metrizoate and metrizamide (150) are presented in Table 4. All patients had normal plasma concentrations of creatinine before angiography. No significant change occurred after angiography. Twelve of the 17 patients in the metrizoate group but none in the ioxaglate group experienced pain. There was a significantly lower intensity of the heat sensation during angiography in the ioxaglate group than in the

metrizoate group (Table 5, the results from paper VI are given for comparison).

Table 4 Urinary Albumin Concentration before and after Renal Arteriography

Contrast Medium	No. of Patients	Concentration of Urinary Albumin (g/g Creatinine)			
		Before Angiography		After Angiography*	
		Median	Range	Median	Range
Ioxaglate	19	0.019	0.006-0.084	0.022	0.006-0.37
Metrizoate†	26	0.029	0.012-0.410	1.1	0.013-36
Metrizamide†	12	0.046	0.003-0.360	0.96	0.011-2.5

* $\frac{1}{2}$ -4 hrs. after arteriography.

† For comparison, the figures from an earlier investigation with metrizoate and metrizamide are presented.

Statistical evaluation: Preangiographic concentration = no significant differences among the 3 contrast media. Postangiographic concentration = ioxaglate: no significant change; metrizoate and metrizamide: significantly increased ($p < 0.005$). No significant difference is seen in the degree of postangiographic albuminuria between metrizoate and metrizamide.

Table 5 VISUAL ANALOGUE SCALE SCORES

Contrast Medium	Visual Analogue Scale Scores (mm)			
	Heat		Pain	
	Median	Range	Median	Range
Renal angiography (V)				
Ioxaglate 280	16	0-56	0	0
Metrizoate 280	70	8-97	8	0-95
Aortocervical angiography (VI)				
Ioxaglate 280	17	6-50	0	0
Ioxaglate 320	23	6-89	0	0-4
Metrizoate 280	76	51-98	0	0
Metrizoate 370	82	21-98	0	0-16

Maximum possible score = 100 mm

TOLERANCE and BIOCHEMICAL EFFECTS FROM INTRAVENOUS INJECTION of IOXAGLATE in HEALTHY VOLUNTEERS /III/

Material and methods Ioxaglate (320 mg I/ml) was injected at a dose of 1 ml/kg body weight (median 60 ml, range 58-90 ml) within one minute into an antecubital vein in 9 healthy volunteers. Precordial ECG and blood pressure were recorded. For analyses of the biochemical parameters, haemostasis and plasma proteins venous blood was sampled sequentially before and 2-4 days

after the injection in 9, 4 and 5 volunteers respectively (see Tables 1, 2 and 3 in paper III) .

Results Some of the biochemical parameters (Hb, EPC, Hct, PPC, Alb, ALAT, AP) were significantly decreased 5 minutes after the injection when compared with the values obtained before the injection. At 30-60 minute after the injection some parameters (Hb, Hct, Alb, AP, Na) were significantly increased as the day after injection (Hb, Alb, Na, LPC). All these changes in biochemical values were within the normal reference range of the laboratory for each parameter except for 2 phosphorous values, which were slightly elevated and were above the normal upper limit on day 1 and 3. All parameters of the coagulation and fibrinolytic systems remained normal except for an increased fibrinolysis that was found in 3 subjects both before and after the injection of contrast medium and in 1 subject only 4 hours after the injection. No fibrinolytic degradation products were found. Two males had a decreased ceruloplasmin value on days 2 and 4 after the injection. One male had slightly elevated values of alpha-antitrypsin, orosomucoid and haptoglobin both before and after injection. Otherwise, no changes were observed during the investigation. No significant changes in blood pressure were recorded. No arrhythmia was detected. At 15 s after the beginning of the injection there was a small but significant decrease in heart rate.

EFFECTS of IOXAGLATE on the LIVER and PANCREAS following SELECTIVE VISCERAL ANGIOGRAPHY in MAN /IV/

Material and methods In 20 patients referred for selective visceral angiography changes in the activities of liver and pancreatic serum enzymes, bilirubin, prothrombin index, and haematocrit were studied sequentially 1-2 weeks before to 6 weeks after angiography (Fig 7). Ioxaglate (280 or 320 mg I/ml) was used as the contrast medium (median total dose 250 ml, range 100-340 ml, median dose/kg body weight 3.5 ml, range 1.3-5.8 ml). Fifteen patients received 2 or more selective visceral injections (median 3.5, range 1-6 injections).

Results Following selective visceral angiography with ioxaglate, no significant elevation occurred in the activities of liver and pancreatic serum enzymes, bilirubin, or prothrombin index within the entire group of patients (Fig. 7). There was a small, but significant, decrease in the measured parameters except prothrombin index immediately after angiography when compared with the values obtained before angiography. No elevation was found in the measured parameters in 14 of the 20 patients. Except for the small decrease in the measured parameters immediately after angiography, a decrease in one or several of the measured enzyme activities was found in 7 of these 14 patients during the observation period. In the remaining 6 of the 20 patients, an increase was recorded in some parameters. No clinically important toxic effect on the liver or pancreas induced by the contrast medium was found.

DEMONSTRATION of the RENAL VENOUS SYSTEM at ROUTINE RENAL ARTERIOGRAPHY / V/

Material and methods The demonstration of the renal veins during routine renal arteriography was retrospectively studied in 60 patients. Twenty-eight patients received metrizoate, 15 metrizamide and 17 ioxaglate. The angiographic procedures and the contrast medium concentration (280 mg I/ml) were the same for all the patients. The quality of demonstration of the renal veins on the angiograms was evaluated according to an arbitrary scoring system (Table 6). AP-films obtained of the renal veins were scored by two radiologists unaware of which contrast medium was used. Both the intrarenal and the main veins were scored.

Table 6

Score	Definition
0	No demonstration
1	Poor demonstration, insufficient for adequate delineation
2	Good demonstration, sufficient for adequate delineation
3	Very good demonstration, high homogenous radiographic density

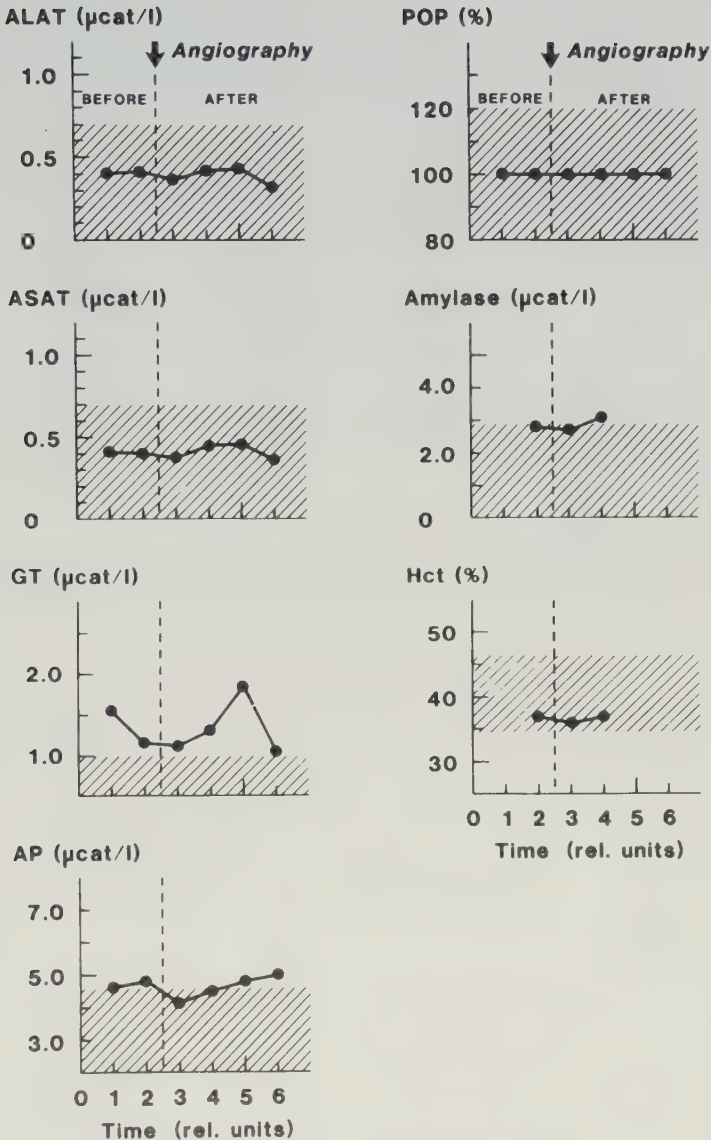


Fig 7 Alterations in the median values of the serum activities of ALAT, ASAT, GT, AP, and prothrombin index (%) pancreatic isoamylase ($\mu\text{cat/l}$), and haematocrit (%) during the observation period. Normal limits for the measured parameters are indicated. Definition of time 1 = days 1–14 before, 2 = immediately before, 3 = immediately after, 4 = day 1 after, 5 = days 2–14 after, and 6 = days 15–46 after angiography.

Results

There was no significant difference between the scores of the intrarenal and main veins. The distribution of the scores is illustrated in Figs. 8 and 9. The renal veins were significantly better and more often demonstrated when ioxaglate was used compared with metrizoate and metrizamide. There was no significant difference between metrizoate and metrizamide. Following semiselective renal artery injection, the main renal veins were demonstrated with a diagnostically acceptable quality with ioxaglate in 76%, with metrizamide in 40% and with metrizoate in 29%. At selective renal artery injection the demonstration of renal veins increased to 85% with ioxaglate and remained unchanged with metrizamide (38%) and metrizoate (26%). In patients who received high dose selective injections of contrast media into arteries supplying a renal tumour ioxaglate resulted in a significant higher frequency of diagnostically acceptable demonstration of the main veins (100%) compared with that of metrizoate (17%). The number of injected kidneys in the metrizamide group was too small to allow a comparison.

AORTOCERVICAL ANGIOGRAPHY

with HIGH and LOW OSMOLALITY CONTRAST MEDIA

A clinical investigation of metrizoate and ioxaglate /VI/

Material and methods Thirty-one patients were investigated and divided into 2 groups. In both groups ECG, arterial blood pressure, subjective responses, occurrence of involuntary movements and image quality were recorded following the different injections. EEG was only recorded in the first group. In group 1 containing 16 patients the first and second injections were made randomly in a double-blind fashion with metrizoate 280 or ioxaglate 280 (280 mg I/ml). In group 2 containing the additional 15 patients the first and second injections were made randomly with metrizoate 370 (370 mg I/ml) or ioxaglate 320 (320 mg I/ml). The third injection was in both groups performed with ioxaglate 320. The angiography started with two indentical lateral angiographic series of the neck at the level of the carotid bifurcation; the only difference was the change of contrast medium. The third series was a lateral projection with a different angulation.

No of injections (%)

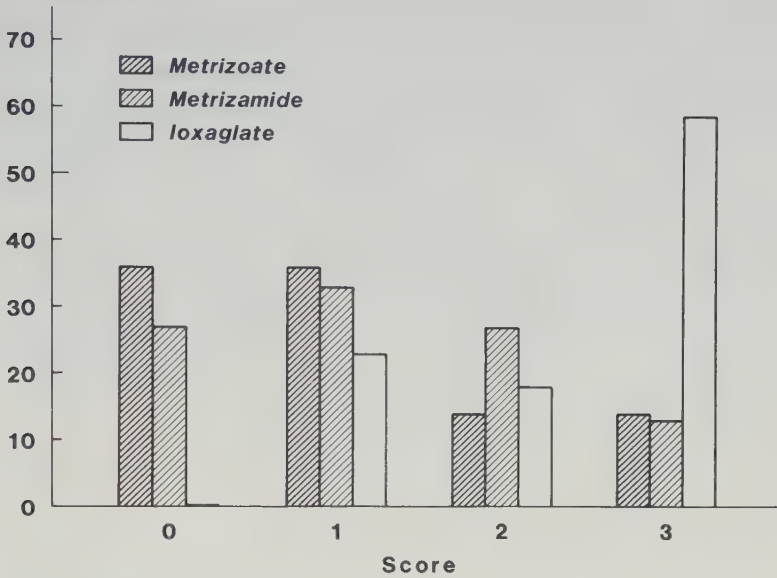


Fig 8

Distribution of the scores of the main renal veins during semiselective arterial injection

No of injections (%)

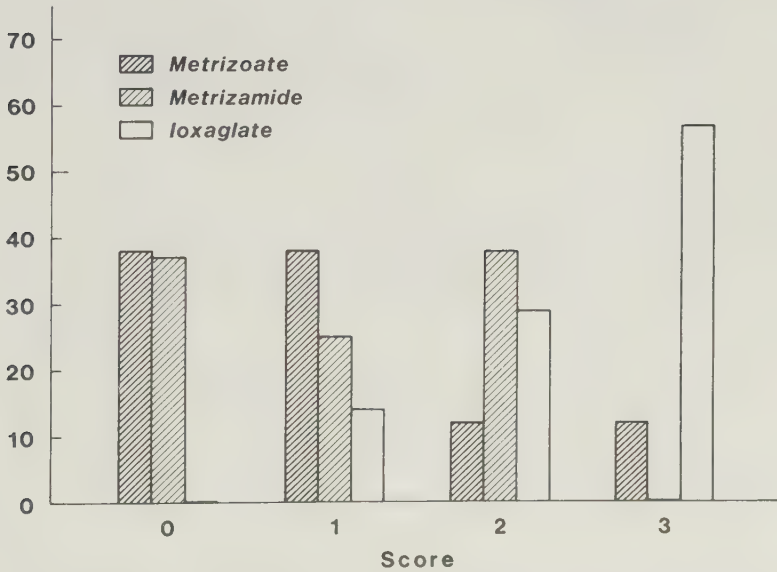


Fig 9

Distribution of the scores of the main renal veins during selective arterial injection

The degree of motion was graphically determined by comparing the film with the best demonstration of the vessels (original key angiogram) with the first film, which was obtained simultaneously with the start of injection. The position of the hyoid bone in relation to the mandible and the hypopharyngeal air column were used as a landmark. The degree of radiographic density and demarcation of the vessels of the carotid bifurcation on both the original key angiogram and the subtraction film was recorded by 2 radiologists according to an arbitrary scoring system (Table 7). Image quality was defined as the sum of these scores. All assessed parameters were evaluated without knowledge of contrast medium or its concentration.

Table 7 Definition of individual score

	Radiographic density	Demarkation
Not diagnostically acceptable	1 low	unsharp
	2 moderate	moderate sharp
Diagnostically acceptable	3 high	sharp
	4 very high	very sharp

Definition of sum of scores

Sum of scores (Image quality)	1-4	Not diagnostically acceptable image quality
	5	Boarderline image quality
	6-8	Diagnostically acceptable image quality

Results There was no significant difference in EEG between the contrast solutions. No significant changes were noted between EEGs obtained the days before and the days after angiography. Brief alterations in EEG recorded during and immediately after the injections appeared in 8 out of 14 patients following all contrast media. In a ninth patient a change in EEG was observed for 20 seconds following metrizoate 280. Only metrizoate 280 induced significant bradycardia (Fig 10). The frequency, the degree and the duration of tachycardia and hypotension was significantly less in both groups following the injection of ioxaglate than of metrizoate. All patients experienced a significantly smaller sensation of heat after injection of ioxaglate

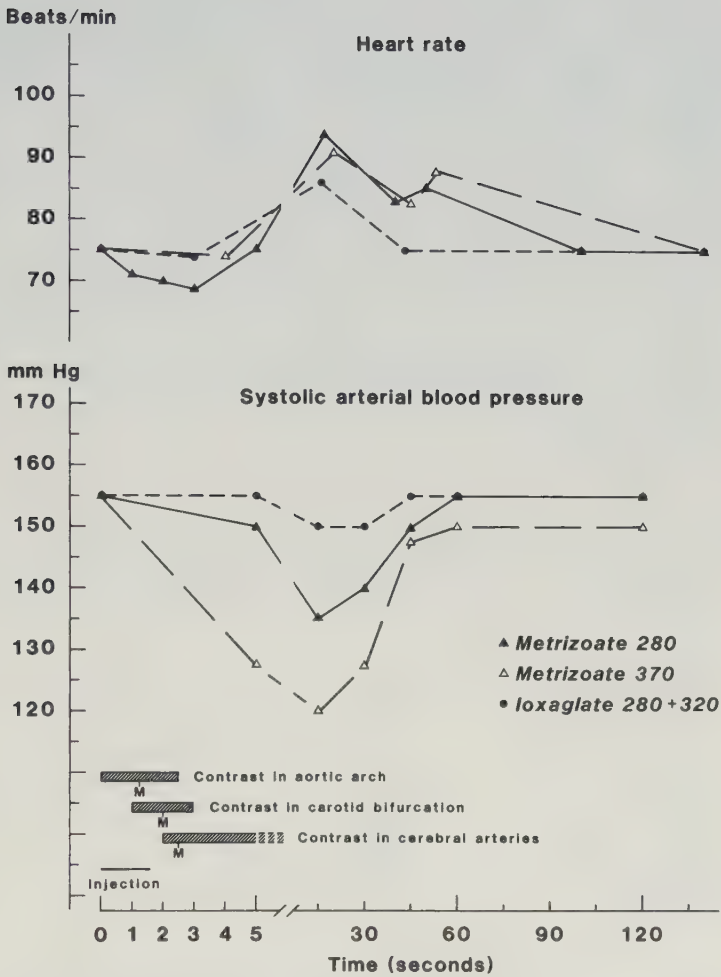


Fig 10

Time-related changes in heart rate and systolic arterial blood pressure (median values) following contrast medium injection into the aortic arch.

M = median time for maximum radiographic density in the vessels

than after metrizoate (Table 5). In group 1 the image quality was equal on the key angiograms between metrizoate 280, ioxaglate 280 and ioxaglate 320 whereas ioxaglate 320 on the subtraction films produced significantly better image quality (Fig. 11). In group 2 the image quality on the key angiogram was significantly better for metrizoate 370 compared with ioxaglate (I) but the image quality on the subtraction film was equal (Fig. 12). The subtraction procedure significantly increased the image quality on the original key angiogram of all contrast solutions except metrizoate 370. Involuntary movements on the key angiogram occurred with no difference in number of patients between the contrast media (Table 8), but late in the film series ioxaglate induced both less pronounced and less frequent involuntary movements.

Table 8

Number of patients with MOVEMENTS during the
entire film series original key angiogram

CONTRAST MEDIUM**GROUP 1**

Metrizoate 28%	14/16	4/16
Ioxaglate 28%	10/16	4/16
Ioxaglate 32%	6/12	2/12

GROUP 2

Metrizoate 37%	12/14	6/14
Ioxaglate 32% (I)	9/14	4/14
Ioxaglate 32% (II)	8/12	2/12

Number of patient regardless of degree reacting with involuntary movements during the entire film series and at original key angiogram (best demonstration of the vessels) following contrast media injection into the aortic arch.

OTHER REACTIONS

Two male participants became nauseated and one of them also vomited during the intravenous bolus injection of ioxaglate (paper III). Otherwise no such reactions was noted in the present series following ioxaglate.

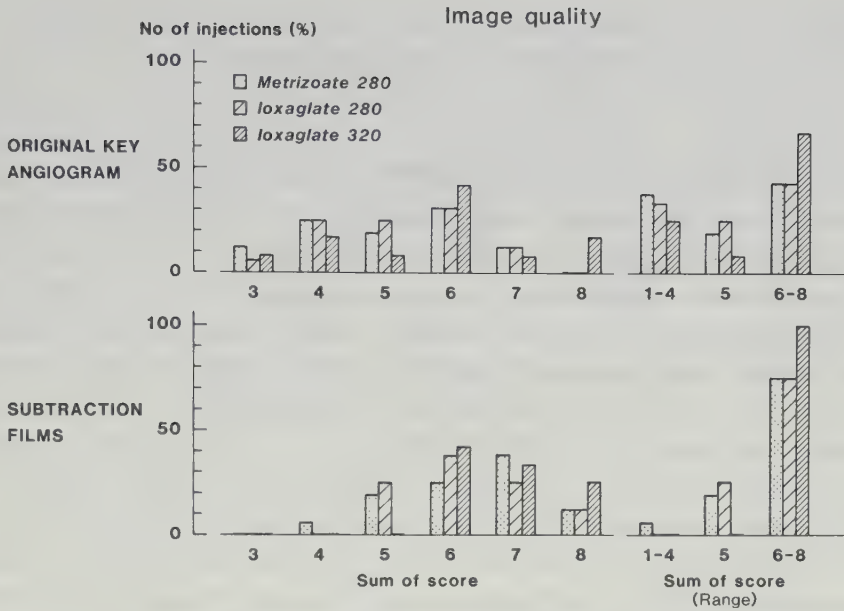


Fig 11 Distribution of the scores of image quality on original key angiogram and subtraction films in group 1. For definition of scores, see table 7

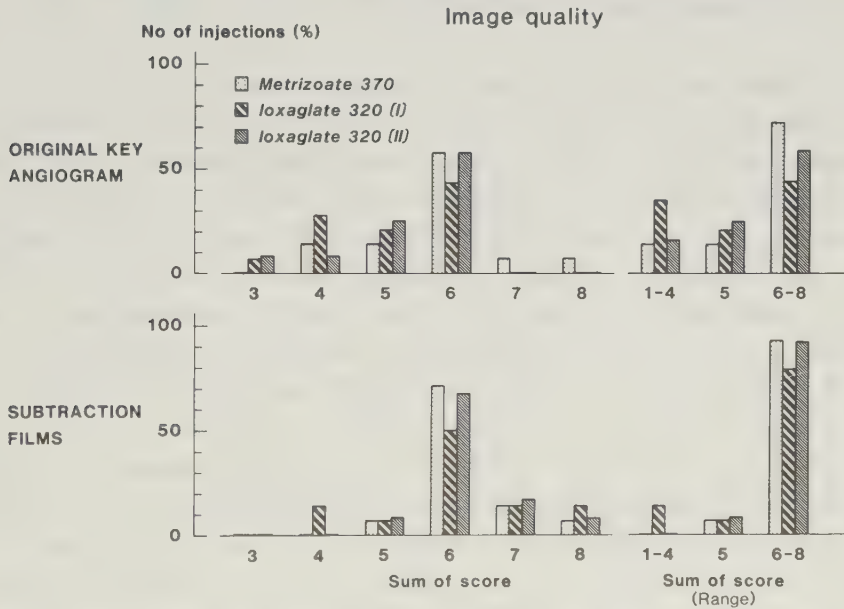


Fig 12 Distribution of the scores of image quality on original key angiograms and subtraction films in group 2

GENERAL DISCUSSION

IOXAGLATE and HAEMODYNAMIC RESPONSE /I,III,VI/

Both clinical and experimental investigations have shown that intraarterial injection of ionic monomeric ratio 1.5 contrast media and other hypertonic solutions into the left ventricle, aorta and extremity arteries produce a fall in peripheral vascular resistance due to vasodilatation, which results in increased blood flow and decreased systemic blood pressure accompanied by an increase in heart rate (31,55-60).

Many of the patients referred for angiography have more or less advanced vascular atherosclerotic disease and limited cardiac reserve. It is unfavourable to expose these patients to marked affliction on the heart and vasculature. These reactions were prominently reduced when the first ratio 3.0 contrast medium, metrizamide, was introduced (61,62) and have been attributed to the reduction in osmolality (57-60).

The present series and other investigations have shown that ioxaglate reduces the vascular reaction similar to that of metrizamide (60,63,64). The pronounced hypotension that most patients in our aortocervical investigation experienced, following metrizoate 370 (osmolality 2150 mmol/kg water) must be considered unfavourable, although we only observed one patient with prominent bradycardia (asystole), hypotension, nausea and vomiting. This patient recovered without sequelae of this occasion. Although the osmolality of the ratio 3.0 contrast media still is hypertonic relative to plasma, sodium chloride solutions in equiosmolal concentration as ratio 3.0 contrast media produce no obvious effects on peripheral vascular resistance (31,58,59). This indicates that the vasodilatory properties of the ratio 3.0 contrast media, besides the osmolality, also are due to a chemotoxic effect. There seems to be no difference in vasodilatory effects between different ratio 3.0 contrast media at equal osmolality (58-60,63-66).

Several of the complications and even deaths that have been reported in angiocardiology have occurred in patients with signs of obstruction in the pulmonary vascular bed (67-68).

Injection of high osmolality contrast media (ratio 1.5) and other hypertonic solutions into the right atrium, ventricle or pulmonary artery induce increase in pulmonary arterial pressure (69-71). This increase in pulmonary arterial pressure has been attributed to increased resistance to blood flow in the pulmonary capillaries due to an increased red cell aggregation or by changes in red blood cell deformability induced by the hypertonicity of the injected solution (72-76).

The dimeric ratio 2.0 iocarmate was shown to induce less influence on pulmonary arterial pressure and also less influence on the red cell morphology and aggregation than the 1.5 contrast media (77). The effect of the ratio 3.0 contrast media are even lower. The present experimental investigation (I) shows that the increase in pulmonary pressure following high dose injection of iohexol and ioxaglate into the right atrium of the rabbit is small. It may be assumed that fewer complications may occur with low osmolality contrast media in angiocardiology (78).

It has become increasingly common to inject contrast media rapidly during high dose bolus urography. These rapid high dose injections through peripheral veins have also increased with computed tomography and digital subtraction angiography. Intra-venous injection of contrast media is generally considered harmless but many adverse reactions to contrast media are observed following these injections. They are often mediated through a cardiovascular collapse. Intravenous injection of ionic monomeric ratio 1.5 contrast media may induce cardiac arrhythmia and hypotension, and even ventricular fibrillation and death (79-87). Katzberg et coll. measured the blood pressure (BP) in patients during urography with ionic monomers and found that 6 % of normal patients developed severe hypotension = BP less than 60 mm HG (88). As a large number of iv injections are performed every day it is important to minimise the risk. In our investigation rapid intravenous bolus injection with ioxaglate in healthy volunteers (III) resulted only in a small transient

decrease in heart rate, in no arrhythmias and in no alteration in BP. High dose injection into an antecubital vein could be considered as a continuous injection into the right atrium of more or less diluted contrast media. The good tolerance of ioxaglate in these regards may reflect its low influence on the heart, pulmonary circulation and peripheral vascular resistance, a result of low osmolality and low chemotoxicity.

IOXAGLATE and SUBJECTIVE RESPONSE /II,III,VI/

The patients' most prominent memory of intravascular radiology especially in peripheral and cerebral intraarterial injections is the pain and heat sensation (subjective response) and these investigations have bad reputation among many patients. The cause of the heat and pain have been attributed to several factors (62,63,89). It has mostly been ascribed to the hypertonicity of the contrast solution (32,33,90,91). The chemotoxicity of the contrast medium may also influence as some authors have shown that different monomeric contrast media induce different pain at equal osmolality (90), but other investigators have not been able to confirm these findings (91). The sodium salts of contrast media (cation) have been suggested to cause more pain than the meglumine salts (91,92). Spech et coll. conclude that the larger the cation molecule, the less painful contrast medium (90). Neither vasodilatation nor electrical charge of the contrast molecule appear to be responsible for vascular-induced pain (90).

A threshold theory exist, claiming that an osmolality above 800 mmol/kg water will result in pain and below only in heat (90,93). The first contrast medium with an osmolality below 1000 mmol/kg water was the non-ionic monomeric ratio 3.0 contrast medium metrizamide. Our investigations (II,III,VI) like other studies (63,94-101) have shown that ioxaglate with an osmolality of about 500 mmol/kg water is comparable to other ratio 3.0 contrast media in inducing pain and heat. The electrical charge of the contrast molecule or the existence of the

cation (sodium and meglumine) does not appear to be of any importance for eliciting subjective response when the osmolality is below 800 mosm. If there exist any difference within the group of ratio 3.0 contrast media, it more likely depends on the difference in osmolality between the contrast media than on the chemical structure. Thus some investigators have found that metrizamide induce less subjective responses than ioxaglate (102) and other found that iohexol and iopamidol induced more than ioxaglate (103,104). This suggest that patients may be able to distinguish an osmolality of 100 mosm. Our results (VI) supports this as 15 out of 16 patients experienced more heat after ioxaglate 320 (osmolality 590) than after ioxaglate 280 (osmolality 480). This is not supprising as 100 mosm corresponds to one third of the normal plasma osmolality.

None of the 9 volunteers in paper III experienced a warmth sensation, which usually appears several minutes after intra-venous injection of ionic ratio 1.5 contrast media. Following rapid intravenous bolus injection this heat sensation can be rather discomfortable and induce anxiety in the patient. As there seems to be a correlation between the patient's anxiety and the frequency of adverse reaction (105), the elimination of the warmth sensation may contribute to less frequent adverse reactions following ratio 3.0 contrast media.

Ever since the introduction of the angiographic procedure in 1923 by Berberich and Hirsch (106), efforts have been made to reduce the painfulness of contrast media by premedication, mixing contrast media with local anesthetics or dilution of the contrast media (107,108). All these procedures have now become unnecessary as the ratio 3.0 contrast media, regardless of they are ionic or non-ionic, nearly totally eliminate the pain and markedly reduce the heat sensation to what some patients express as "mild comfortable warmth". At our department we only use low osmolality contrast media in angiography and the investigations have become "silent".

IOXAGLATE and TOLERANCE

Toxic effects following intravenous bolus injection /III/

Ionic monomeric ratio 1.5 contrast media may, when injected into the circulation, disturb fluid and electrolyte balance, interfere with coagulation and fibrinolytic systems, activate complement compounds, acidify plasma, interact with serum protein and enzymes, release biologically active substances, and affect blood cells and platelets (18-24). Most of these side effects have been shown to occur more often in vitro and less often in vivo and several of them have been suggested to cause systemic toxic reactions induced by contrast media (25-29).

These adverse effects can be explained partly by the hypertonicity and partly by the chemotoxicity of the contrast medium. However, any direct correlations between these individual factors and the clinical reaction have not been proved (109,110).

Ioxaglate may also induce such effects, like other ratio 3.0 contrast media, and in some instances to a lesser degree than ratio 1.5 contrast media (109-119). We investigated the influence of intravenous injection of ioxaglate (III) on various biochemical, coagulation and fibrinolytic parameters, and fractionated plasma proteins in healthy volunteers. Despite a brief and small decrease in some biochemical parameters 5 min after the injection, which may be due to haemodilution induced by the hypertonicity of the contrast medium, we found no clinically significant changes. This is in accordance with other investigations on non-ionic ratio 3.0 contrast media (120-122).

Table 2 shows the LD₅₀ values of some ionic and non-ionic contrast media (30). The possible clinical importance of these differences in acute general toxicity between various contrast media has extensively been discussed by Almén (30).

Several factors such as low general toxicity and low osmolality indicate that the ratio 3.0 contrast media may induce less severe adverse reaction than the ratio 1.5 (30,113,123,124). The severe adverse effects are thus most likely due to both the hypertonicity and the chemotoxicity of the contrast media.

Mild adverse effects as nausea and vomiting, seems also to appear more frequent following ratio 1.5 contrast media (125,126) and may be due to other factors e.g. the ionicity of the contrast media. The fact that the ionic contrast media are more toxic when injected intrathecally (127), probably reflects the toxicity of the carboxylgroup, supporting this hypothesis. The nausea and vomiting may be eluciated in the brain as the blood-brain-barrier is abscent in the area postrema (128) and local extravasation in this region may activate the centra of nausea and vomiting in sensitive patients.

Some authors have found a tendency that also ioxaglate induces as much nausea and vomiting as the ionic ratio 1.5 media (129,130) but other investigations have not been able to confirm these findings (125,126). In the present serie 2 of 9 volunteers become nauseated following intravenous bolus injection but the number of subjects are too few to allow any conclusion as regards the frequency of this type of side effect. Otherwise no systemic toxic reaction, severe or mild, was seen in any of the investigations on humans in this investigation.

Effects on the liver and pancreas following selective visceral angiography /IV/

Previous experimental and clinical investigations with monomeric ionic ratio 1.5 contrast media indicate that selective visceral angiography is a safe method. Non or only a small, but statistically significant, increase in serum activity of liver enzymes has been reported after selective visceral arterial injection in animals (131-136) and man (133,137,138). Selective visceral angiography with the non-ionic metrizamide and iohexol induced minimal toxic effects on the liver in animals (46,136) and in man (139,140) and no toxic effects were shown on pancreas in man (139,140). We found (IV) that selective visceral angiography with ioxaglate induced no clinically important toxic effects. Our results support the findings that selective visceral angiography is a safe procedure in patients both with and without impaired liver and/or pancreatic function.

Effects on the kidney following renal arteriography /II/

Acute renal failure (ARF) resulting from the use of monomeric ionic ratio 1.5 contrast media is an increasing problem, and is one of the most serious adverse reactions to contrast media (141-144). The mechanism behind the ARF produced by contrast media are poorly understood and the cause may be multifactorial (141-144). Contrast media may produce different responses in the kidney such as changes in renal blood flow, glomerular filtration rate (GFR) and filtration fraction (FF) (145-148). These effects have been ascribed as toxic effects or physiological adaption to changes induced by the contrast media. The influence of contrast media on the kidneys can be measured in many ways. We have investigated postangiographic proteinuria. Proteinuria is a sign of renal injury indicating increased glomerular permeability. Holtås et coll. have previously found that transient albuminuria frequently occurred following renal angiography with monomeric ionic ratio 1.5 contrast media but also following metrizamide in both humans and dogs (149-152). In experiments with dogs, ioxaglate and iohexol induced a small increase in urinary albumin levels (153) whereas our investigation (II) and another on iohexol (154) in man showed no significant increase in postangiographic urinary albumin concentration.

Other investigations have shown that ioxaglate and iohexol may induce postangiographic proteinuria in the rat but not in the rabbit and the same complex renal tolerance for other contrast media have been found (155-157). There thus seems to exist a species specificity and the relevance of animal investigations to humans in this aspect is doubtful. On the human kidney however iohexol and ioxaglate appear to produce very little proteinuria following renal angiography why we assume that these ratio 3.0 contrast media may be less toxic to the glomeruli than other agents.

Effects on the brain following aortocervical angiography /VI/

Ioxaglate is not developed to be use in the subarachnoidal space. Intrathecally injected it is more toxic than the non-ionic compounds (127). Injected into the circulation ioxaglate has shown to penetrate the blood-brain-barrier less than the ionic monomers and to an equal degree compared to the non-ionic compounds (158,159). During selective cerebral angiography no clinically important toxic reactions to the brain have been observed (104,160-163). In our aortocervical investigation (VI) we found brief transient changes in EEG during the injections following all contrast media. These may be explained by the fact that the blood in the arteries supplying the brain is exchanged with more or less diluted contrast media and may for a short time influence the exchange of oxygen and glucose to the brain. The toxic influence of contrast media on the brain may also be evaluated by the degree of bradycardia and hypotension induced by the contrast media (54,164-167). Ioxaglate produced no bradycardia or no hypotension when injected into the aortic arch. Thus ioxaglate did not induce any significant toxic effects during aortocervical angiography.

IOXAGLATE and IMAGE QUALITY /V,VI/

When only the hypertonic ratio 1.5 contrast media were available no major difference what concerns diagnostic usefulness was proved except some considerations about the importance of high or low viscous contrast media in cerebral and coronary angiography (168,169). In the field of contrast media nearly all research have been focused on the toxicity and the high osmolality of the ratio 1.5 contrast media. The introduction of the ratio 3.0 contrast media solved many of these problems. It is the opinion of mine that no major improvements will be achieved in further reducing omolality of contrast media. The new field for research may be image quality and this will demand a specific contrast medium for each type of investigation e.g.

different osmolality, different iodine concentration, different diffusion properties, ionic versus non-ionic etc according to the specific needs of the examination (170).

In the present series we found that ioxaglate better demonstrated the renal veins than metrizoate and metrizamide during routine renal angiography (V). We have also shown that during aortocervical angiography (VI) metrizoate 370 produced the best image quality on the original angiograms but ioxaglate 320 produced as good image quality if subtraction technique was used. Thus this indicates some differences between various contrast media as regards image quality and diagnostic usefulness, also between the ratio 3.0 contrast media.

In our evaluation of image quality at aortocervical and renal angiography different methods have been used. In the aortocervical investigation we used intraindividual random injection in a double-blind fashion during two identical projections making the patient his own control (171). In the renal vein study only one contrast medium was used in each patient. It could be assumed to be more preferable to use a study design like that of the aortocervical study with two or several injections of different contrast media in random order into the same kidney. Little is however known about the influence of the first injection into the renal artery on the next injection and furthermore we know that different contrast media induce different responses in the kidney, as proteinuria and changes in renal blood flow (145-149).

To estimate the degree of image quality in the 2 investigations we used an arbitrary score system. In paper V and VI efforts were made to translate the scores into clinical terms as diagnostic acceptable versus not diagnostic acceptable. The accuracy of our score system is supported by the results of an experimental study that found a significantly higher concentration of ioxaglate in the renal veins compared with metrizoate, diatrizoate and the non-ionic contrast media iohexol and iopamidol (172).

The difference in image quality between the contrast media was more pronounced in the investigation of the renal veins (V)

than in the investigation of the vessels of the head and neck (VI). In this investigation (VI), however, all factors that could influence image quality, except for the contrast media, were held constant. The possibility to distinguish between small differences in image quality may be questioned. Every arbitrary scoring system for evaluation of image quality is based on a high degree of subjectivity. We were, however, able to register statistically significant differences between the different contrast solutions.

Different factors influenced by contrast media may affect the image quality such as involuntary movements, iodine concentration, viscosity and diffusion.

ioxaglate and involuntary movements /VI/

At aortofemoral angiography it is obvious that the pain and heat induced by the contrast medium leads to motion artifacts and poor image quality. When the pain sensation are less pronounced as in aortocervical investigation (VI) no difference was found in the degree of involuntary movements during the first seconds = the time to obtain the key angiogram. Thus other factors may be more important than the choice of contrast medium. We have suggested that the procedure per se and the noise from the equipment may be more important.

ioxaglate and iodine concentration /VI/

Earlier, during conventional angiography, the main opinion has been: The more iodine the better image. We found that with the film system and exposure data used in our conventional aortocervical angiography an iodine concentration of 370 mg I/ml was optimal, but that a concentration of 320 mg I/ml of a contrast medium with low osmolality and high viscosity was equally suitable if subtraction technique was used.

ioxaglate and viscosity /V,VI/

The viscosity of a contrast medium bolus may influence image quality. Two different values of viscosity are important. The viscosity of the contrast medium per se and the viscosity within the admixed fluid (blood + contrast media) in the vessels. The viscous response of blood to contrast medium is more related to its hypertonicity than to its viscosity (73,173). We have in paper VI suggested that not only an increase in iodine concentration but also an increase in viscosity may be responsible for the increased image quality when comparing metrizoate 370 or ioxaglate 320 with metrizoate 280 (Table 3). The explanation can be that a high osmolality of the contrast solution increases the effective viscosity inside the aortic arch and thereby influencing image quality. This may be due to a smaller degree of turbulence (inversely correlated with the degree of viscosity). A high viscosity of the injected contrast solution may also result in a more coherent bolus causing better radiographic density at the carotid bifurcation. As a result the flow will be low along the inside of the vessel resulting in a better demarcation.

Contrast media chilled down to 5 ° C in order to increase the viscosity have been used at conventional intravenous angiography for cardiovascular investigation. Good tolerance and sufficient image quality was reported (174).

Most companies developing contrast media try to avoid high viscous solutions mainly because there are difficulties in injecting the solutions. This is only valid for injections into peripheral veins. During arteriography, modern catheters and pressure injectors easily inject even high viscous compounds.

ioxaglate and diffusion rate /V/

Ioxaglate demonstrated the renal veins during routine renal angiography better than metrizoate and metrizamide. We assume that renal arteriography with ioxaglate in most cases could replace or exclude renal venography. From the results in our investigation the conclusion can be made that if the renal venous system is unaffected, a semiselective injection with ioxaglate

demonstrates the veins.

We have advanced the hypothesis that the results in Paper V are due to differences in diffusion rate between the three investigated contrast media. It must here be emphasized that the hypothesis is based on considerations of current facts of kidney physiology and of the diffusion of small molecules in the hind-leg of the dog but also to some degree from human and dog kidney (see addendum page 46), which together with the results of the present work (V) and that of Morris et coll. (172) have been synthesized to a hypothesis.

I assume that the differences in viscosity and osmolality between the three investigated contrast media (Table 3) are not the major explanation to the results in paper V because the kidney is normally adapted to high viscosity and high osmolality (175-179). Instead I consider that differences in diffusion rate is the explanation because diffusion is a very fast process and the diffusion rate for small molecules across capillary walls is normally overwhelmingly greater than the filtration process (180-188). Probably most of the diffusion of the contrast molecules takes place in the postglomerular capillaries where the total surface area is much greater than in the glomeruli. Furthermore the blood pressure and flow in these capillaries are much lower than in the renal arteries (175-179). Table 9 gives the diffusion rates of some substances with different molecular weight (183).

From these facts I have assumed that the heavier, high viscous and low osmolality contrast medium ioxaglate has a slower diffusion rate in the vascular space in the kidney than metrizoate and metrizamide.

The considerations about different diffusion rate of contrast molecules are not new. In 1966 Almén published theoretical considerations (189) about the diffusion rate of macromolecules. In 1969 Björk, Erikson and Ingelman (32) mentioned in connection with their work on polymers of contrast media the possibility of low diffusion rate for some contrast media and they found in 1976 (190) a good demonstration of the renal veins with a poly-

mer (MW about 4000). Furthermore already in 1962 Theander and Wehlin (191) and Edling and Ovenfors (192) showed that a good demonstration of the renal veins was obtained by using non-ultrafiltrable contrast media. These authors suggested that a better demonstration of the renal veins was due to shorter capillary nephrographic phase and that these contrast media could not be eliminated immediately by the kidneys into the glomerular ultra-filtrate. The reason is more likely that large molecules are heavily restricted in their diffusion across the capillary walls.

Investigators (193) have suggested continuous selective injections in very high doses of contrast medium (50 ml) but only if it is obvious that the kidney are to be removed. The explanation why single bolus injection of about 50 ml with monomeric ontrast media gives rise to a good demonstration of the renal veins may be that the extravascular space (EVS) is saturated by the first part of the contrast bolus resulting in a lower concentrationgradient over the capillary wall. The remaining contrast bolus escapes the capillaries more slowly, which results in an high iodine concentration in the renal veins. This assumption is in accordance with an experimental study in dogs that showed an improved demonstration of the renal veins when fractionated selective injection of contrast media was performed. The best result was obtained when doses of about 2 + 6 ml, with an interval of five seconds, was injected. However the results in paper V suggest that at least injection with metrizoate in doses of about 25 ml does not seem to be enough to saturate the EVS in renal carcinoma probably because of the increase in EVS that is found in tumours (195).

GENERAL SUMMARY and CONCLUSIONS

Investigations of the effect of the monoacidic dimeric low osmolality, ratio 3, contrast medium ioxaglate are described on

Haemodynamic response and tolerance during Renal, selective visceral and aortocervical angiography, and intravenous bolus injection in man and angiocardiology in rabbits.

Subjective responses during lumbar aortography, aortocervical angiography and intravenous bolus injection in man.

Image quality during renal and aortocervical angiography,

Ioxaglate caused significantly less haemodynamic responses than metrizoate; less subjective responses than metrizoate; less postangiographic proteinuria than metrizoate and metrizamide; better demonstration of the renal veins than metrizoate and metrizamide.

Ioxaglate produced equal haemodynamic responses as iohexol during angiocardiology in rabbits; equal image quality as metrizoate during aortocervical angiography; no clinically important toxic effects following renal, selective visceral and aortocervical angiography and intravenous bolus injection.

Ioxaglate proved to better demonstrate the renal veins than metrizoate and metrizamide during renal arteriography. It is a heavier molecule than the monomeric contrast media suggesting that the molecular size and weight and thereby the degree of diffusion rate across capillary walls may be of importance for the diagnostic usefulness.

Ioxaglate was found to be well suited for intravascular use.

PERSONAL CONSIDERATIONS

The existence of different diffusion rate of small substances may be usable in the further development of new contrast media in trying to improve the diagnostic usefulness. As shown in the papers of Landis, Pappenheimer and Renkins, and Chinard et coll. (176,178,180-183), concerning transcapillary exchange of small molecules in the hindleg or the kidney of dogs, it may be inferred that inulin (MW 5000) acts very similar to greater molecules such as albumin (MW 67000). Furthermore there are considerable difference in diffusion rates (diffusion coefficients) between molecules with MW of 25-600 in the hindleg of the dog. The work of Chinard et coll. (182) indicates that these differences is even greater in the kidney and is also valid for greater molecules than those with MW 600. I have performed some recalculations of the results from Landis and Pappenheimer (183) as shown in Table 9 and Fig. 13.

Table 9

substance	Molecular weight	Specific permeability	
		cm sec ⁻¹ 10 ⁵	relative to that for inulin
water	18	28	93
NaCl	58	15	50
Urea	60	14	47
Glucose	180	6	20
Sucrose	342	4	13
Raffinose	594	3	10
Inulin	5100	0.3	1
Myoglobin	17000	0.1	
Albumin	67000	0.001	

Permeability of 100 g mammalian muscle capillaries to lipid insoluble molecules, recalculation from Landis and Pappenheimer (183)

I assume that a current monomeric contrast medium has a MW of about 600. It is then obvious from Fig 13 that e.g. tri- or tetrameric compounds (MW > 1800) may have even slower diffusion rate (and lower osmolality) compared to mono- and dimeric compounds. As most membranes are negatively charged it may be favourable, in this regard, if the contrast agent is charged. An intensified development of polymeric contrast media higher than the dimeric seems justified.

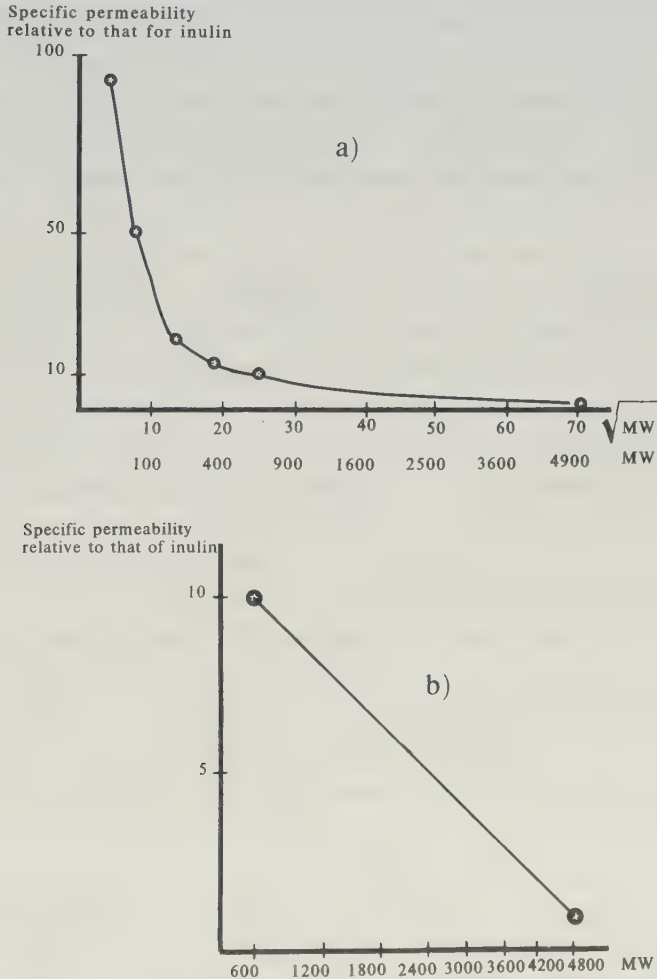


Fig 13

Specific permeability of 100 g mammalian muscle capillaries to lipid insoluble molecules relative to that of inulin (5100 MW), recalculation from Landis and Pappenheimer (183) a) 0-100 times b) 0-10 times The theoretical molecular weight (MW) for polymers (x 600 MW) of monomeric (600 MW) contrast media with molecular weights between 600 - 4800 e.g. 1200, 2400, 3000 etc. are indicated

ADDENDUM

The hypothesis advanced about the differences in diffusion rate of contrast media in the kidney are based on the following facts:

Current physiological facts of the kidney (175-179): The blood pressure in the renal artery and afferent capillaries equals the systemic arterial blood pressure (SABP). The blood pressure decreases rapidly in the efferent capillaries and is about 15 - 20 % that of the SABP in the peritubular capillaries. The blood flow is high in the cortex but the medullary blood flow is only 10 - 20 % of the cortical. The total surface area of the postglomerular capillaries is about 10 times that of the glomerular capillaries. The extravascular volume (EVS) excluding the tubular volume in one human kidney per 1.73 m² has been calculated to about 50 ml, the renal blood volume to 35 ml, total exchangeable water content to 150 ml, tubular cell volume to 95 ml and interstitial volume to 30 ml. The peritubular tissue and plasma are hypertonic due to the filtration process and the counter current mechanism. The osmolality (up to 2100 mmol/kg water) can even exceed that of ratio 1.5 contrast medium solutions. The blood viscosity in the postglomerular vessels and predominately in the vasa recta may be several times that of systemic blood viscosity partly because of concentration of plasma protein due to the ultrafiltration process and mainly because of crenation of erythrocytes induced by the high plasma osmolality, a result of the close functional relationship of the vascular compartments to the counter current mechanism of urine concentration.

Current facts about diffusion (180-185): Diffusion is a very fast process that follows the laws of thermodynamics. The diffusion rate is for small molecules (e.g. smaller than inulin) across capillary walls normally overwhelmingly greater than the filtration rate. Plasma water exchanges 120 times per min with the interstitial water (immediately surrounding the capillaries) and for glucose the exchange occurs 30 times per min. The diffusion of water, NaCl, urea and glucose back and forth through

the capillary wall occurs at rates which are, respectively, 40, 20, 18, and 10 times the rate at which these substances are brought to the tissues by incoming blood. On a single circulation in the kidney approximately 90 % of the water entering the renal artery crosses the walls of the renal capillary systems. Lower but still substantial values of the diffusion coefficient and the volume of diffusion have been found for other substances. In contrast, the extravascular circulation of fluid caused by net filtration and absorption is only 2 per cent of the plasma flow. For this reason the rates of exchange of small molecules between blood and tissues are but little affected by simultaneous net fluid movements. The same concentration difference which causes the diffusion also gives rise to the observed osmotic pressure.

Two types of diffusion of molecules may occur: free diffusion in the solvent within the vessels and a restricted diffusion across the vessel wall. According to Fick's first law of free diffusion (186) and the modifications made by Sutherland and Einstein (187,188), the free diffusion of molecules in a solution at a constant temperature is dependent on 1) the concentration gradient within the solution, 2) the viscosity of the solution, and 3) the molecular radius of the molecules in solution. The restricted diffusion of molecules through pores in the capillary walls depends on 1) the concentration gradient across the capillary wall, 2) the viscous drag at the wall, 3) the molecular size, and 4) the electrical charges of the molecules and the pores of the vessel wall.

Doktorshandledning modell 1984

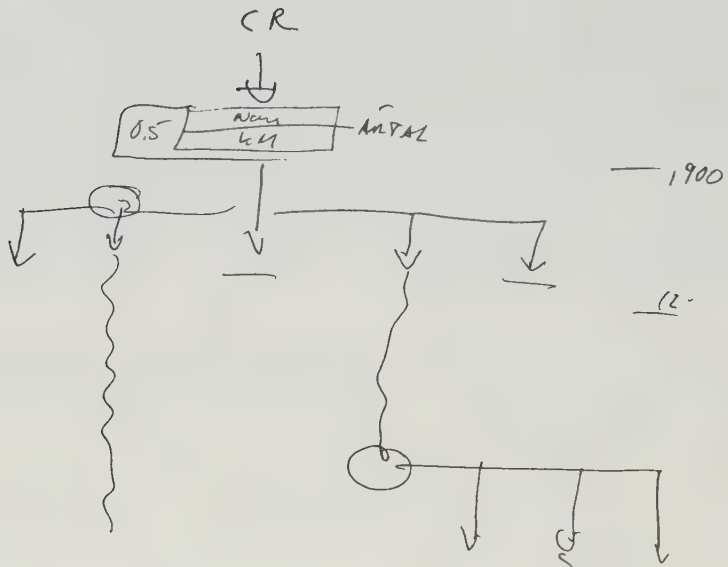


Fig 1A

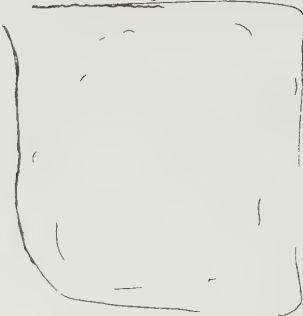
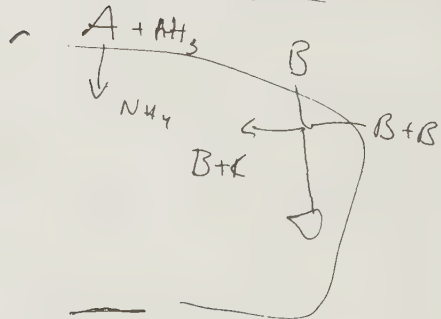


Fig B.



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FROM THE DEPARTMENTS OF EXPERIMENTAL RESEARCH AND DIAGNOSTIC RADIOLOGY, MALMÖ ALLMÄNNA SJUKHUS, S-21401 MALMÖ, SWEDEN.

AORTIC AND PULMONARY ARTERIAL PRESSURE AFTER INJECTION OF CONTRAST MEDIA INTO THE RIGHT ATRIUM OF THE RABBIT

Comparison between metrizoate, ioxaglate and iohexol

TORSTEN ALMÉN, PETER ASPELIN and PAUL NILSSON

Several complications, and even deaths have been reported, following injection of contrast medium into the right atrium (DOTTER & JACKSON 1950, Cournand et coll. 1953, DIMOND & GONLUBO 1953, ELDRIDGE et coll. 1955, ROWE et coll. 1956, EMANUEL 1961).

Many of these patients had obstruction of pulmonary vessels (DOTTER & JACKSON, DIMOND & GONLUBO, EMANUEL, SNIDER 1973).

Numerous experiments have shown that contrast medium injected into the right atrium, ventricle or pulmonary artery induces an increase in pulmonary arterial pressure both in animals and in man (BINET & BURSTEIN 1951, ROWE et coll., ELIAKIM et coll. 1958, READ 1959, WATSON 1964, FRIESINGER et coll. 1965). It has been assumed that this increase in patients with pulmonary vascular diseases has been an etiologic factor to some of these complications. It has also been shown that the elevation in pulmonary arterial pressure is augmented with increasing osmolality of the injected contrast medium (ALMÉN & ASPELIN 1975, ALMÉN et coll. 1975). It was demonstrated that, following injection into the right atrium, the non-ionic contrast medium metrizamide which has a lower osmolality in iodine equivalent concentration than currently used ionic monomeric media, also induced less increase in pulmonary arterial pressure than these media.

The effects of iohexol on aortic and pulmonary arterial pressure following injection into the right atrium of rabbits have now been investigated and

compared with those of ioxaglate and metrizoate. Ioxaglate is an ionic monoacidic dimeric medium which like iohexol in iodine-equivalent concentrations has a lower osmolality than metrizoate.

Technique

Twelve rabbits of both sexes weighing 2.5 to 3.5 kg were used. They were anaesthetized with pentobarbitone and atropine sulphate intravenously (1 mg atropine sulphate for each 30 mg of pentobarbitone). The animals were placed supine. Throughout the experiments they were breathing spontaneously through a tracheostomy. Three catheters (Medioplast No. 13) were inserted. One from a jugular vein into the right atrium for injection of contrast medium, one from a jugular vein into the pulmonary artery or out-flow tract of the right ventricle for pressure recordings and one from a femoral artery into the descending thoracic aorta for pressure recordings. Pressure recordings were made on a Mingograf.

The following solutions, all with an iodine content of 370 mg I/ml, were injected into the right atrium of the heart: the ionic monomeric contrast medium metrizoate (Isopaque Coronar, Nyegaard & Co. A/S) osmolality 2.15 mol/kg, viscosity 8.4 mPa · s at 37°C, the monoacidic dimeric contrast medium ioxaglate (Hexabrix, Laboratoire Guerbet) viscosity 16.5 mPa · s at 37°C, and the non-ionic contrast medium iohexol (Nyegaard & Co. A/S) osmolality 0.98 mol/kg, viscosity 13.4 mPa · s at 37°C.

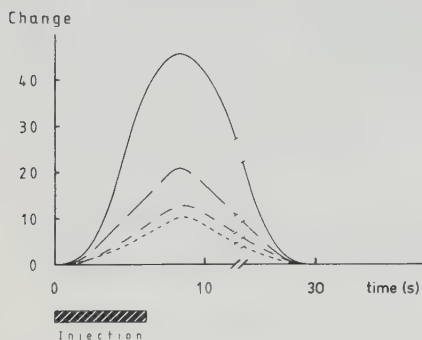


Fig. 1. Changes (per cent) in pulmonary arterial systolic pressure following injection of contrast medium into the right atrium of rabbits. The curves represent the median values presented in Table 1. Metrizoate (—), ioxaglate (---), iohexol (---), physiologic saline (-.-).

The chemical structure of the contrast media have been given by HAAVALDSEN (1980).

All media were injected at 37°C and in a volume of 3 ml/kg body weight. The time of injection was 3 to 15 seconds with a variation of one second or less in each individual rabbit. All rabbits received one injection of all 3 contrast media in random order with an interval of 15 min between the injections. In 5 of the rabbits an additional injection of physiologic saline was given.

Measurements. Throughout each experiment the pulmonary and aortic pressures changed regularly with the respiration. The systolic pressure measured in the pulmonary artery or the out-flow tract of the right ventricle and the systolic pressure in the aorta were the parameters of interest. The pressures were continuously recorded for half a minute before injection and 3 min after injection. The systolic pressure in the out-flow tract of the right ventricle and the main stem of the pulmonary artery was equal and is in the following called pulmonary arterial systolic pressure. Following the injection of the different media into the right atrium, the pulmonary systolic pressure increased and reached a maximum within 10 seconds from the start of the injection. This maximum increase is expressed in per cent of the highest pulmonary systolic pressure obtained during a half-minute-period before the injection.

The changes in aortic systolic pressure following injections of the test solutions are described as early changes, occurring during the first 12 seconds after the start of the injection and late changes, occurring

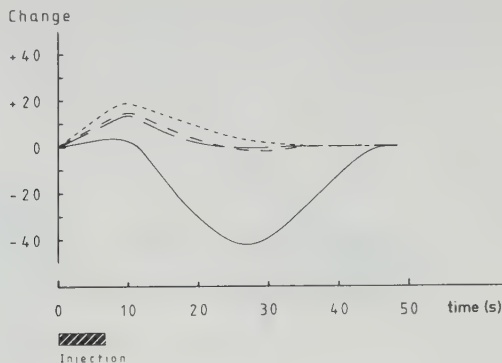


Fig. 2. Changes (per cent) in aortic systolic pressure following injection of contrast medium into the right atrium of rabbits. The curves represent the median values presented in Tables 2-3. (Symbols as in Fig. 1.)

15 to 25 seconds after the start of the injection. The increase in aortic pressure is expressed in per cent of the highest systolic pressure during half a minute before injection. The decrease in aortic pressure is expressed in per cent of the lowest aortic systolic pressure during half a minute before the injection.

Statistical analysis was made according to Wilcoxon's test for paired differences. A *p*-value less than 0.01 was considered significant.

Results

The effects on pulmonary arterial and aortic pressures following the injections into the right atrium appear in Figs 1 and 2 and in Tables 1 to 3.

Pulmonary arterial pressure. All the injected solutions increased the pulmonary arterial pressure. Iohexol and ioxaglate caused significantly less increase than metrizoate. No differences between iohexol, ioxaglate and saline were found.

Aortic pressure. All the injected test solutions increased the early systolic aortic pressure. No differences existed between iohexol and ioxaglate and the pressure changes produced were similar to those produced by saline. The increase in early systolic aortic pressure following injection of Isopaque Coronar was significantly smaller than that of iohexol and ioxaglate. The late systolic aortic pressure was decreased significantly more after metrizoate than after iohexol and ioxaglate. No differences between iohexol, ioxaglate and saline were found.

Table 1

Maximum increase in pulmonary arterial systolic pressure following the injection of test solutions into the right atrium

Test solution	Median value (per cent)	Range
Metrizoate	+46	+17-+88
Iohexol	+13.5	0-+33
Ioxaglate	+21	+5-+38
Physiologic saline	+10	0-+33

Table 2

Maximum change in early systolic aortic pressure following injection of test solutions into the right atrium

Test solution	Median value (per cent)	Range
Metrizoate	+2.5	-63-+11
Iohexol	+14.5	+7-+32
Ioxaglate	+13	0-+32
Physiologic saline	+18	0-+33

Table 3

Maximum change in late systolic aortic pressure following the injection of test solutions into the right atrium

Test solution	Median value (per cent)	Range
Metrizoate	-42.5	-72--24
Iohexol	-1	-10-+23
Ioxaglate	0	-12-+25
Physiologic saline	+8	0-+18

Discussion

Following the injection of contrast media into the right atrium of rabbits, the contrast media iohexol and ioxaglate with low osmolality caused less increase in pulmonary arterial pressure than metrizoate with high osmolality. This observation corresponds well with previous findings (ALMÉN & ASPELIN). Also a difference in aortic pressure occurred, metrizoate with high osmolality induced greater changes in aortic blood pressure than the two contrast media with low osmolality when compared with the changes induced by saline. This is in agreement with previous observations (ALMÉN & ASPELIN).

The exact mechanism behind the increase in pulmonary arterial pressure following the injection of

hypertonic solutions into the right atrium is not known. It has been attributed to arterial spasm (BINET & BURSTEIN), venous spasm (ELIAKIM et coll.), nerve reflexes (INGLESBY et coll. 1972) or to increased resistance at the level of the pulmonary capillaries (SEMLER et coll. 1959). However, recent investigations (ASPELIN 1978 a, b, 1979, ASPELIN & SCHMID-SCHÖNBEIN 1978) indicate that the hypertonic solutions produce changes in the red blood cell rheology which may induce the increased pulmonary arterial pressure. These authors demonstrated that the red cells in contact with hypertonic contrast media solutions become rigidified to the extent that these cells in vitro do not pass through pores with the same diameter as that of the nutrient capillaries. These results imply that it is the rigidified red cells that block the capillaries and, secondarily to the reduced flow, an increased red cell aggregation may take place. These two effects on red cell rheology may thus explain the increase in pulmonary arterial pressure. It was also shown that the contrast media inducing the least rigidification (those with the lowest osmolality) also induced the least increase in pulmonary arterial pressure.

The assumption that the rigidified red cells may be the cause of the increase in pulmonary arterial pressure is in accordance with the findings of EFFROS (1972), who found that the injection of hypertonic solutions markedly impaired red cell transit time through the lungs which became much longer than the transit time of plasma that remained unchanged.

The present results support these previous investigations in which the osmolality of the contrast media was found to be the most important factor influencing the changes in pulmonary arterial pressure that follows the injection of contrast media into the right atrium.

The mechanisms discussed, through which the resistance to flow through the lungs was increased by hypertonic solutions, might also explain the early changes in aortic blood pressure. Thus, Isopaque Coronar which has the highest osmolality is assumed to cause a higher increase in resistance to blood flow through the lungs than ioxaglate and iohexol. This results in a lower flow through the lungs to the left side of the heart and consequently a smaller output from the left ventricle. The latter induces a smaller increase in aortic pressure compared with the injection of the same volume of saline into the right atrium. The increase in early

aortic pressure following the injection of the saline solution was regarded as a volume effect of the injected solution.

Concerning the late changes in aortic pressure, which did not occur until the contrast medium had reached peripheral branches of the systemic circulation, it is well known that contrast medium solutions are potent vasodilators and that this property is related mainly to their osmolality. Also other factors, such as chemotoxicity, are of importance (HILAL 1966, LINDGREN et coll. 1968). This is in accordance with the present results where the late decrease in aortic systolic pressure was significantly smaller after the injection of ioxaglate and iohexol than after metrizoate.

As some of the complications and deaths in cardioangiography have been related to an increase in pulmonary arterial pressure, the new contrast media of low osmolality (iohexol, ioxaglate) should be tried clinically for the purpose of cardioangiography with the intention of decreasing the risk of this procedure, especially in patients with diseases in the pulmonary vascularity.

SUMMARY

Effects in cardioangiography from injections into the right atrium of rabbits of two new contrast media of low osmolality, one non-ionic (iohexol) and one ionic dimeric (ioxaglate), were recorded and compared with a currently used ionic contrast medium (metrizoate) of high osmolality. Iohexol and ioxaglate produced significantly smaller increase in pulmonary arterial pressure than metrizoate. Also in aortic pressure iohexol and ioxaglate induced smaller changes (compared with the injection of the same volume of saline) than metrizoate.

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Subjective Responses and Albuminuria Induced by Ioxaglate during Renal Angiography in Man¹

The degree of albuminuria induced by renal arteriography with the monoacid dimeric contrast medium ioxaglate was studied in 19 patients. Ioxaglate did not cause significant changes in urinary albumin concentrations (median concentration after angiography = 0.022 g/g creatinine). The results with ioxaglate are compared with those of an identically designed study performed earlier with the contrast media metrizoate and metrizamide, in which both caused significantly increased concentrations of urinary albumin (1.1 g/g creatinine and 0.96 g/g creatinine, respectively). The degree of pain/heat sensation following semiselective renal arteriography with metrizoate and ioxaglate was also compared using a visual analog scale in 34 patients. Ioxaglate caused no pain and a significantly lower heat sensation than metrizoate.

Index terms: Contrast media, comparative studies • Contrast media, complications

Radiology 144: 509-512, August 1982

ACUTE renal failure (ARF) resulting from the use of conventional tri-iodinated contrast media is an increasing problem, and is one of the most serious adverse reactions to contrast media. It was reported that in some renal treatment centers (1), about 12% of the cases of ARF were induced by drugs, and 40% of those were caused by radiographic contrast media. There was an unnegligible mortality associated with those cases. In the last five years the number of reports of ARF following the administration of contrast media such as diatrizoate, iothalamate, metrizoate, and iopanoic acid has rapidly increased (2-8).

Proteinuria is a sign of renal injury, and it has recently been found that transient proteinuria frequently occurs following renal arteriography with the ionic contrast materials metrizoate and diatrizoate and with the nonionic contrast material metrizamide both in humans and dogs (9-11). The concentration of urinary albumin can reach extremely high values after renal arteriography, and urinary concentrations higher than those in plasma have been observed (8-13). There is also strong evidence that postangiographic proteinuria has been involved in the development of ARF (8). The high osmolality of the contrast agent has not been considered to be the most important factor causing proteinuria (12); the chemical structure seems to be more important (9-11, 13, 14).

One aim of the present investigation was to estimate the degree of albuminuria induced by renal arteriography in humans with the new monoacid dimeric contrast medium ioxaglate and to compare it with the albuminuria induced by metrizoate and metrizamide, which has been previously investigated (9).

The ionic contrast materials commonly used today induce a pain/heat sensation and often cause the patient great discomfort when they are injected during arteriography (15). The degree of such a pain/heat sensation seems to be correlated strongly with the osmolality of the contrast medium (15). Recently, new contrast media with low osmolality, such as metrizamide and ioxaglate, were shown to cause considerably fewer painful reactions in patients undergoing peripheral and carotid arteriography (15-18, 21).

Another aim of this investigation was to compare the degree of pain/heat sensation induced by renal arteriography with the contrast media metrizoate and ioxaglate.

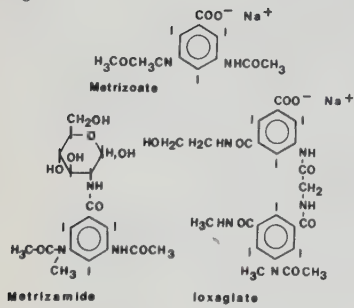
METHODS

Study of Albuminuria

Changes in urinary albumin concentration following routine

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Figure 1



Chemical structure of metrizoate, metrizamide, and ioxaglate.

renal arteriography with the contrast medium ioxaglate were studied in 19 patients (median age 55 yrs., range 32-83 yrs.).

Figure 1 shows the chemical structure of ioxaglate, TABLE I describes the physical and chemical data, and TABLE II lists the amount of contrast medium used in the investigation. The most frequent diagnosis was renal cancer. Other common diagnoses were renal cysts, nephrosclerosis, and pyelonephritis.

Angiography: Selective renal arteriography and lumbar aortography (semiselective technique) were performed with polyethylene catheters (O.D./I.D. = 2.2/1.45 mm). Thirty milliliters of contrast material was injected with an automatic pressure injector (Medrad, Mark IV) in aortography (20 ml/s) and 10 to 12 ml in selective renal arteriography (6-8 ml/s). In the 6 patients in whom a malignant tumor was found, an additional continuous injection of 20 to 30 ml (rate 8-10 ml/s) was made into the artery supplying the tumor. In these 6 patients, celiac angiography (40 ml, 10 ml/s) and, in one patient, superior mesenteric angiography (40 ml, 10 ml/s) were also performed in a search for liver metastases.

TABLE I: Physical and Chemical Data for Ioxaglate, Metrizoate, and Metrizamide

Data	Ioxaglate	Metrizoate	Metrizamide
Trade name	Hexabrix	Isopaque Cerebral	Amipaque
Firm	Lab. Guerbet, Paris, France	Nyegaard & Co A/S, Oslo, Norway	Nyegaard & Co A/S, Oslo, Norway
Iodine content (mg/ml)	280	280	280
Number of iodine atoms/ Number of particles in solution	6/2 = 3	3/2 = 1.5	3/1 = 3
Viscosity: 20° C cP	8.7	7.2	9.7
37° C cP	4.8	4.0	5.0
Osmolality (mosm/kg water)	490	1,460	460

Sampling and analysis: Plasma and urine specimens were obtained before and as soon as possible after angiography (about 1/2-4 hrs.). In 10 patients specimens were also obtained the day after angiography. All samples were frozen and kept at -20°C until analysis. The concentrations of creatinine and albumin were determined in all samples. The analyses were performed as previously described (19). The urinary albumin concentration was determined by immunological methods and the concentration was expressed per gram of urinary creatinine, thereby relating albumin excretion to the glomerular filtration rate. Comparisons in the degree of postangiographic albuminuria induced by ioxaglate and that induced by metrizoate and metrizamide in an earlier investigation (9) were based upon the concentration in the sample taken 1/2 to 4 hours after angiography.

Study of Pain/Heat Sensation

In 34 patients the pain/heat sensation during semiselective renal arteriography (catheter with 6 sideholes and the tip placed in one of the renal arteries) was studied. Thirty milliliters of contrast medium (20 ml/s) was injected

in every patient. Seventeen of the patients (median age 66 yrs., range 30-77 yrs.) received metrizoate and 17 (from the same group of patients in whom the present study of albuminuria was conducted) received ioxaglate. The patients' only premedication was a 10-mg diazepam suppository. The only anesthesia was mepivacaine (Carboanest), locally injected at the puncture site around the femoral artery.

The reactions of heat/pain were measured with a visual analog scale, and the patients were asked to note the degree of pain/heat with a pencil (17, 21). The analog scale consisted of a 100-mm-long line with the left end signifying "no pain" or "no heat" and the right end "unbearable pain" or "unbearable heat." There was one line for pain and one for heat. The patients' notes were measured in millimeters and the results following injection of metrizoate and ioxaglate were compared.

Statistical Analyses

For the statistical analyses, the Mann-Whitney rank sum test or Wilcoxon test for pair differences was used. Differences were considered significant when *p* values less than 0.05 were obtained.

TABLE II: Amount of Contrast Medium Used

Contrast Medium	No. of Patients	Total Amount Given to Patients (ml)		Total Amount Given to Both Kidneys (ml)		Total Amount Given Selectively to One Kidney (ml)	
		Median	Range	Median	Range	Median	Range
Ioxaglate	19	155	75-300	38	20-99	28	12-62
Metrizoate*	26	150	90-265	42	6-80	18	5-75
Metrizamide*	12	150	30-230	54	5-99	22	5-82

* For comparison, the doses injected in an earlier investigation of metrizoate and metrizamide are presented.

RESULTS

Postangiographic Albuminuria

Following renal arteriography with ioxaglate, no significant change occurred in the concentration of urinary albumin. The concentration in the samples taken the day after angiography in 10 patients did not differ significantly from the preangiographic concentration. The median and range of urinary albumin concentration before and after renal arteriography are given in TABLE III.

All patients had normal plasma concentrations of creatinine before angiography (upper normal limit 115 $\mu\text{mol/l}$ for men and 100 $\mu\text{mol/l}$ for women). No significant change occurred after angiography.

Patients' Reaction to Pain/Heat

Twelve of the 17 patients in the metrizoate group experienced pain, but none in the ioxaglate group did. There was a significantly lower intensity of the heat sensation during angiography in the ioxaglate group than in the metrizoate group ($p < 0.005$). TABLE IV gives the median and range of visual analog scores in both groups.

DISCUSSION

Renal arteriography with currently used contrast media, such as metrizoate, diatrizoate, and metrizamide, induces transient albuminuria, which is often massive in both experimental animals and humans (8-11, 13). The proteinuria is mainly a result of increased glomerular permeability caused by the contrast medium (19).

The present results show that renal arteriography with ioxaglate does not induce albuminuria in humans, whereas it has been shown in an earlier investigation that massive postangiographic albuminuria is induced by both metrizoate and metrizamide (TABLE III). The present investigation and the investigation concerning metrizoate and metrizamide were identically designed and were performed at the same laboratory to make a comparison possible. There were no significant differences in angiographic routines, amount of contrast medium (TABLE II), or indications for angiography in the two investigations. The urinary albumin levels before arteriography did not differ significantly

TABLE III: Urinary Albumin Concentration before and after Renal Arteriography

Contrast Medium	No. of Patients	Concentration of Urinary Albumin (g/g Creatinine)			
		Before Angiography		After Angiography*	
		Median	Range	Median	Range
Ioxaglate	19	0.019	0.006-0.084	0.022	0.006-0.37
Metrizoate†	26	0.029	0.012-0.410	1.1	0.013-36
Metrizamide†	12	0.046	0.003-0.360	0.96	0.011-2.5

* $\frac{1}{2}$ -4 hrs. after arteriography.

† For comparison, the figures from an earlier investigation with metrizoate and metrizamide are presented.

Statistical evaluation: Preangiographic concentration = no significant differences among the 3 contrast media. Postangiographic concentration = ioxaglate: no significant change; metrizoate and metrizamide: significantly increased ($p < 0.005$). No significant difference is seen in the degree of postangiographic albuminuria between metrizoate and metrizamide.

TABLE IV: Visual Analog Scale Scores

Contrast Medium	No. of Patients	Visual Analog Scale Scores (mm)*			
		Heat		Pain	
		Median	Range	Median	Range
Ioxaglate	17	16	(0-56)	0	0
Metrizoate	17	70	(8-97)	8	(0-95)

* Maximum possible score = 100 mm.

among the patients receiving the different contrast media.

In the investigation concerning metrizoate and metrizamide, 3 of the 26 patients in the metrizoate group and 2 of the 12 in the metrizamide group had slightly elevated concentrations of creatinine in their plasma before angiography (105, 114, and 151 $\mu\text{mol/l}$, and 112 and 152 $\mu\text{mol/l}$, respectively). However, all of the other patients had normal concentrations, as did all of the patients in the present investigation. Thus, the great discrepancy in the degree of postangiographic albuminuria cannot be explained by this fact. One of the patients with an elevated plasma creatinine level who was injected with metrizoate reacted with an increase of the creatinine concentration from 151 to 263 $\mu\text{mol/l}$. Two weeks after angiography the concentration had returned to the preangiographic level. Otherwise there were no changes in creatinine concentration in either the present study or the earlier study.

In experiments with dogs ioxaglate induced a minor increase in urinary albumin levels (13). The reason for this discrepancy in results between dogs and humans could be that the glomerular filtration of albumin normally is much greater in dogs than it is in humans (22) or that the concentration of contrast medium was higher (370 mg I/ml) in the dog experiments.

In the investigation concerning metrizoate and metrizamide in humans (9), no correlation was found between

the dose of contrast medium and the degree of postangiographic albuminuria, whereas such a relationship was found in dogs when diatrizoate was injected (11). This could probably be explained by the different ways of altering the dose of contrast medium injected selectively into the renal arteries. In the present investigation the variation in dose was based mainly on variation in the number of injections and not on a standardized change in the volume of contrast medium, as it was in the dog study. Therefore, no valid comparison was possible between the two studies. It has been suggested that single injections of large volume in dogs are more injurious to the kidney than repeated small injections (9).

Postangiographic proteinuria has a rapid onset, with a maximum concentration within the first hours after angiography and normalization usually occurring within 24 hours (11, 19). The present investigation was not designed to study the time relations of postangiographic albuminuria more closely, since this was earlier studied thoroughly in dogs. In those experiments, it was shown that the maximum urinary level of albumin often appeared within 15 minutes after the injection of contrast medium into the renal arteries (11). It was therefore considered sufficient to analyze the urine obtained the first time the patient spontaneously evacuated the bladder, which occurred $\frac{1}{2}$ to 4 hours after angiography. As a

control, additional urine specimens were taken the day after angiography in 10 patients. There were no significant differences in the urinary albumin concentration between the two post-angiographic specimens.

The osmolality of the nonionic contrast medium metrizamide is about one third that of the ionic contrast media metrizoate and diatrizoate at equal iodine content. However, the degree of postangiographic albuminuria induced by renal arteriography with these three contrast media did not differ significantly in earlier investigations in humans or dogs (9–11). Furthermore, a sodium chloride solution with the same osmolality as diatrizoate induced significantly less albuminuria than the contrast medium (12). Consequently, high osmolality does not seem to be a major factor causing albuminuria.

In dogs it was shown that four low low-osmolality contrast media, the nonionic iohexol, iopamidol, and C 29, and the ionic dimeric ioxaglate, caused significantly less albuminuria than diatrizoate (13). The fact that one low-osmolality contrast medium (metrizamide) induces massive albuminuria, whereas four other low-osmolality contrast media (iohexol, iopamidol, C 29, and ioxaglate) do not, shows that the chemical structure of the contrast medium is more important than its osmolality.

It is essential to cause patients as little discomfort as possible during the angiographic procedure. Furthermore, the reduction of pain and heat sensations during the injection of the contrast medium will reduce the movements of the patient and thereby reduce the risk of poor radiographic quality. The degree of local pain and heat sensation seems to be highly correlated with the osmolality of the contrast medium (15, 16, 18). This is confirmed in the present study showing significantly lower pain/heat sensation for patients undergoing angiography with ioxaglate than for those undergoing angiography with metrizoate.

The visual analog scale was used for comparison of the patients' pain/heat sensations in the present investigation because it appears to be a more reliable method of reflecting the actual pain/heat sensation than other verbal rating scales. It is also a convenient method for statistical evaluation (16, 20).

The risk of inducing renal failure with conventional compounds is probably small in patients with normal

kidney function, although contrast media such as diatrizoate, metrizoate, and metrizamide frequently induce massive postangiographic proteinuria. However, in patients with other risk factors, such as diabetes mellitus, severe arteriosclerosis, transplanted kidneys, and hypertension, and in patients with impaired renal function before angiography, the risk of causing ARF is probably higher. For this reason it is important to use a contrast medium that affects the kidney function as little as possible. Proteinuria is a sign of renal injury and might in some cases be involved in the development of ARF. Contrast media intended for renal arteriography should therefore be those least likely to induce proteinuria. If pain and heat sensation could be reduced at the same time it would be a great advantage. The present investigation shows that it is possible to avoid postangiographic proteinuria and to lower the pain/heat sensation during renal arteriography by using the monoacid dimeric contrast medium ioxaglate.

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TOLERANCE AND BIOCHEMICAL EFFECTS FROM INTRAVENOUS INJECTION OF IOXAGLATE IN HEALTHY VOLUNTEERS

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Abstract

The influence of intravenous injection of ioxaglate (Hexabrix, 320 mg I/ml) on various biochemical, coagulation and fibrinolytic parameters, fractionated plasma proteins, precordial ECG and blood pressure was prospectively and sequentially studied in 9 healthy volunteers. One ml/kg body weight of the contrast medium was injected within one minute into an antecubital vein. Small, but statistically significant, changes in some of the biochemical parameters were found during the observation period, 2 to 4 days. All values of the biochemical parameters were, however, within the normal reference range for each parameter. No significant alterations were seen in the coagulation parameters. Increased fibrinolysis was recorded in some subjects both before and after the injection. No fibrinolytic degradation products were found indicating that the fibrinolysis was nominal. No significant changes were observed in the fractionated plasma proteins. The heart rate decreased significantly 15 seconds after commencing the injection. No significant changes in blood pressure were recorded. Two participants became nauseated and one of them vomited during the injection. Apart from this, no adverse effects were noted. No clinically significant changes following the injections were found.

Ionic monomeric contrast media (diatrizoate, iothalamate, and metrizoate) have disadvantages when injected into vessels; they disturb fluid and electrolyte balance, interfere with coagulation and fibrinolytic systems, activate complement compounds, acidify plasma, interact with serum protein and enzymes, release several biologically active substances, and affect blood cells and platelets (1, 3,

17, 19, 20, 35, 41). These effects can be explained partly by the hypertonicity (5–7 times that of human plasma) and partly by the chemotoxicity of the contrast medium (11).

In order to reduce the toxicity of contrast media, compounds with lower osmolalities have been developed, i.e. the non-ionic monomeric metrizamide, iohexol, iopamidol, and the ionic dimeric ioxaglate.

Tolerance and biochemical effects induced by intravenous injection of metrizamide and iohexol in healthy volunteers have been reported (2, 22).

Ioxaglate has not been investigated in a similar way. Hence, the aim of our investigation was to study the influence of intravenous injection of ioxaglate on various biochemical, coagulation and fibrinolytic parameters, fractionated plasma proteins, precordial ECG and blood pressure in healthy volunteers.

Material and Methods

The investigation was performed during March 1982. Ioxaglate (Hexabrix, Laboratoire Guerbet, Aulnay-sous-Bois) was injected within one min into an antecubital vein in 9 healthy volunteers (5 women and 4 men, median age 33 years, range 23–42 years). The volunteers were in the supine position 10 min before to 15 min after the injection. The injection was made at room temperature, at a concentration

Table 1

Median values of biochemical parameters in 9 volunteers before and after intravenous injection of ioxaglate

Biochemical parameters	Normal reference range	Before injection	Time after injection			
			5 min	30–60 min	Day 1	Days 2–4
Hemoglobin (Hb)	115–166 g/l	128	125*	135**	133**	139
Erythrocyte count (EPC)	3.7–5.4 $10^{12}/l$	4.2	4.2*	4.4	4.4	4.6
Leukocyte count (LPC)	4–10 $10^9/l$	5.6	5.4	5.9	6.4**	6.3
Leukocyte differential count						
Neutrophils (N)	18–67 %	50	51	54	56	51
Eosinophils (E)	0–6 %	2	1	2	1	2
Basophils (B)	0–1 %	1	0	1	0	0
Lymphocytes (L)	14–40 %	37	36	35	34	39
Monocytes (M)	2–9 %	7	7	6	6	6
Erythrocytes (Eryth)	Normal=n	n	n	n	n	n
Hematocrit (Hct)	35–48 %	39	37*	40**	39	41
Platelet count (PPC)	125–340 $10^9/l$	230	225*	245	265	265
Erythrocyte sedimentation rate (ESR)	2–24 mm	4	5	4	4	4
Sodium (Na)	136–146 mmol/l	141	142	142**	143**	141
Potassium (K)	3.5–5.0 mmol/l	4.1	4.1	4.4	4.2	4.2
Creatinine (Creat)	60–115 $\mu\text{mol}/l$	84	80	82	82	91
Albumin (Alb)	40–52 g/l	44	40*	45**	45**	46**
Calcium (Ca)	2.20–2.60 mmol/l	2.39	2.27	2.41	2.39	2.41
Phosphorus (P)	0.70–1.30 mmol/l	1.09	1.08	1.11	1.25	1.15
Bilirubin (Bil)	<20 $\mu\text{mol}/l$	<20	<20	<20	<20	<20
Aspartate-aminotransferase (ASAT)	<0.67 $\mu\text{cat}/l$	0.42	0.47	0.47	0.58	0.48
Alanine-aminotransferase (ALAT)	<0.67 $\mu\text{cat}/l$	0.29	0.17*	0.27	0.27*	0.30
Alkaline phosphatase (AP)	<4.6 $\mu\text{cat}/l$	2.3	2.1*	2.4**	2.4	2.4
Glutamyl transferase (GT)	<1.0 $\mu\text{cat}/l$	0.19	0.16	0.20	0.29	0.30
Uric acid (URAT)	120–480 $\mu\text{mol}/l$	262	261	238	296	265
Glucose (Glc)	3.5–5.0 mmol/l	4.6	4.5	4.9	4.4	4.3

* Statistically significant decrease, $p < 0.05$.** Statistically significant increase, $p < 0.05$.

of 320 mg I/ml and at a dose of 1 ml/kg body weight (median 60 ml, range 58–90 ml). At this iodine concentration, the osmolality is 580 mmol/kg water. One ml of the ioxaglate solution contains 196.5 mg sodium ioxaglate, 393 mg meglumine ioxaglate and 0.1 mg sodium calcium edetate.

Blood samples. For analyses of the biochemical parameters (Table 1), venous blood was sampled immediately before the injection of the contrast medium and 5, 30–60 min, and 1 and 2–4 days after the injection in all 9 volunteers.

For analyses of the haemostasis, samples were collected one day before and 30 min and 4 h after the injection in 4 volunteers.

For analyses of the plasma proteins, venous blood samples were taken immediately before and 2–4 days after the injection in 6 volunteers.

The blood samples were analysed at the Depart-

ments of Clinical Chemistry and Coagulation Disorders, Malmö General Hospital, according to procedures described previously (7, 10, 14, 16, 21, 28, 29).

ECG and blood pressure. An ECG lead I rhythm strip was recorded continuously before, during and for 10 min after the injection of ioxaglate. Blood pressure was measured immediately before, at the beginning of the injection and then at 30 s, 1, 2, 3, 4, 5 and 10 min after the injection.

Adverse effects. The participants were observed for 8 h after the injection and any adverse reactions during a follow-up period of 2 weeks were recorded. The volunteers were not restricted as regards to food and fluid during the investigation.

Statistical evaluation. For the statistical analyses, the Wilcoxon signed rank test for paired differences was used. p -values less than 0.5 were considered to be significant.

Table 2

Measured parameters of the coagulation and fibrinolytic system and obtained values in 4 volunteers (median and range)

Analysis	Normal reference range	Before inj. median (range)	30 minutes after inj. median (range)	4 hours after inj. median (range)
Bleeding time according to Ivy	6–12 min	6 (5–7)	6 (5–7)	5 (4–7)
Activated partial thromboplastin time	<45 s	31 (27–32)	31 (28–32)	31 (28–32)
Platelet count	125–340 $10^9/l$	250 (205–265)	245 (215–260)	250 (240–275)
Prothrombin time	14–17 s	15.9 (15.2–16.0)	16.0 (15.3–16.2)	16.0 (15.6–16.1)
Factor VIII related antigen (VIII R; Ag)	45–170 %	95 (60–180)	95 (55–160)	105 (55–160)
Owren's prothrombin-proconvertin assay	60–140 %	105 (94–120)	99 (84–118)	94 (79–116)
Fibrinogen	2.5–4.0 g/l	2.8 (2.6–3.6)	2.8 (2.8–3.5)	2.8 (2.7–3.2)
Fibrinolytic activity on fibrin plate				
Citratd plasma	24±35 mm ²	25 (0–64)	10 (0–20)	15 (0–51)
Resuspended euglobin precipitation	98±54 mm ²	163 (64–220)	177 (57–206)	192 (182–204)
Euglobin clot lysis time	>150 min	100 (60–220)	205 (90–360)	85 (70–105)
Fibrinogen degradation products	<5 mg/l	<5	<5	<5
Ethanol gelation test	Negative	Negative	Negative	Negative

Table 3

Measured fractionated plasma proteins and values obtained in 6 volunteers (median and range)

Protein	Normal reference range (g/l)	Immediately before injection median (range)	Day 2 or 4 after injection median (range)
Albumin	40–52	46 (40–53)	46 (40–54)
Alpha-antitrypsin	0.90–1.70	1.33 (1.22–1.94)	1.37 (1.19–1.74)
Orosomuroid	0.55–1.05	0.65 (0.47–1.01)	0.72 (0.58–1.13)
Haptoglobin	0.45–2.75	1.32 (0.92–1.77)	1.63 (0.97–2.68)
Cerulolasmin	0.22–0.48	0.29 (0.23–0.53)	0.30 (0.18–0.77)
Immunoglobulin G	7–15	10 (8–12)	10 (9–12)
Immunoglobulin A	0.5–3.0	1.2 (0.5–2.4)	1.4 (0.8–2.0)
Immunoglobulin M	0.4–2.0	0.7 (0.4–1.0)	0.7 (0.5–1.0)

Results

Biochemical parameters (Table 1). The values of haemoglobin, erythrocyte count, haematocrit, platelet count, albumin, ALAT and AP were significantly decreased 5 min after the injection when compared with the values obtained before the injection. Haemoglobin, haematocrit, albumin, AP and sodium were significantly increased 30–60 min after the injection. The day after injection, haemoglobin, albumin, sodium, and leukocyte count were significantly increased, but ALAT decreased. During days 2–4, albumin still remained significantly increased. The platelet count was increased 30–60 min, on day 1 and on days 2–4 after the injection, but the increases were not statistically significant. All the mentioned

changes in values were within the normal reference range of the laboratory for each parameter except for 2 phosphorous values, which were slightly elevated and were above the normal upper limit on day 1 and 3 (1.60 and 1.65 $\mu\text{mol/l}$) in one male and on day 3 (1.37 $\mu\text{mol/l}$) in one female.

Coagulation and fibrinolytic system (Table 2). An increased fibrinolysis was found in 3 subjects both before and after the injection of contrast medium and in one subject only 4 h after the injection. No fibrinolytic degradation products were found in any volunteer. All other parameters remained normal.

Fractionated plasma proteins (Table 3). Two males had a decreased ceruloplasmin value on days 2 and 4 after the injection (0.18 and 0.19, respective-

ly). One male had slightly elevated values of alpha-antitrypsin, orosomucoid and haptoglobin both before and after injection. Otherwise, no changes were observed during the investigation.

ECG, blood pressure and adverse effects. No significant changes in blood pressure were recorded. No arrhythmia was detected. After the beginning of the injection there was a small decrease in heart rate (median maximum decrease 7 beats/min, range 2–13, median time 30 s, range 15–180 s) followed by an increase (median maximum increase 9 beats/min, range 2–51, median time 75 s, range 30–300 s). The changes in heart rate were only statistically significant for the decrease 15 s after the injection began.

Two male participants became nauseated and one of them also vomited during the injection. Both reacted with tachycardia (maximum increase in heart rate 36 and 51 beats/min, respectively). In one, the blood pressure remained normal and in the other, who vomited, the blood pressure could not be measured 1 and 2 min after the injection.

Discussion

Intravenous bolus injection of currently used hypertonic ionic monomeric contrast media may in clinical use induce ECG changes, arrhythmias and even death (30, 36). Experimental and clinical studies have shown that intravenous injection of hypertonic contrast media induce significantly more haemodynamic effects than low osmolality compounds (12, 38). In the present investigation the new low osmolality compound ioxaglate caused no change in blood pressure and only a small, but statistically significant, decrease in heart rate 15 s after the start of the injection, which accords with one previous investigation (38). The change in heart rate was considered clinically insignificant.

In vitro studies have shown an increase in serum osmolality, reduction of water content, decrease in haematocrit, haemoglobin, potassium and sodium about 5 to 10 min after the injection of hypertonic ionic monomeric contrast media. Following this small increase the values usually normalize within 15–30 min (23). In our investigation the values of haemoglobin, haematocrit, erythrocyte count, platelet count, albumin, ALAT and AP decreased 5 min after the injection and were sometimes followed by an increase at 30 and 60 min. Such changes were also observed in the investigations on metrizamide

and iohexol (2, 22). These changes can be explained by a haemodilution partially due to alterations in the hydrostatic pressure when the subject changes from the standing to the supine position and the changes are partially induced by the hypertonicity of the contrast medium. The haemodilution is then followed by a haemoconcentration (13), which also can be due to changes in plasma volume induced by alterations in the subjects position and/or the diuretic effect of the contrast.

On the days after the injection, statistically significant changes in some biochemical parameters were found, but these were small and within the normal reference range for the method. The small increase in platelet count, leukocyte count and in albumin are notable, as similar changes were observed in the investigation of iohexol (22). In that investigation no similar corresponding change was found in the samples that were obtained from the control group who received saline. These changes were ascribed to random deviations which could be observed after determination of a large number of laboratory parameters. Another explanation may be that contrast medium influences the platelets (41) and leukocytes (6). A relatively small amount of dehydration may be induced, as the albumin value was increased for several days.

It has been demonstrated that ionic monomeric contrast media may cause a reduction in ionic calcium both in vivo and in vitro. This effect has been ascribed to both the contrast medium molecule and the additives, such as edetate and citrates (25, 39). Ioxaglate has also been reported in vitro to reduce (26, 39) and not reduce (4, 40) ionic calcium. In our in vivo investigation no change in the total serum calcium level was found.

Elevated phosphorous values were seen the day after the injection in 2 subjects. This may be explained by a contamination of the samples with heparin or edetate.

All the reported changes in biochemical parameters are considered to be clinically insignificant. Interaction and disturbance of the coagulation and fibrinolytic systems or in the platelet aggregation capacity have been recorded in vitro using high concentrations of contrast media (18, 24, 33, 41), and in vivo using large doses of contrast media (4, 20, 33, 35, 41). Some of these changes have been reported to be due to the cation in the contrast medium, i.e. sodium or meglumine (18, 24). Ioxaglate has also been reported to interfere with the

coagulation and fibrinolytic system and platelets both in vitro and in vivo (4, 9, 27, 32, 37). The reported changes were transient and did not induce any disturbances of clinical importance. Our work did not reveal any changes in coagulation and fibrinolytic parameters, although the ioxaglate solution contains both meglumine and sodium as cations. However, a slight fibrinolysis was found in some subjects before and after the injection of ioxaglate which might be explained by a stress reaction caused by the procedure. No fibrinolytic degradation products were found, indicating that the fibrinolysis was inappreciable.

Different opinions in the literature exist regarding alterations of the electrophoretic protein pattern induced by contrast media (17, 31). Our investigation did not reveal any alterations in the electrophoretic protein pattern.

One of our subjects reacted with nausea, but did not vomit. He had tachycardia (121 beats/min), elevated phosphorous value, an increase in platelet count on days 1 and 3 ($350 \times 10^9/l$ and $410 \times 10^9/l$), slightly elevated alpha-antitrypsin, orosomucoid and haptoglobin values before and after the investigation. This subject had had a mild infection during the week before the injection, which may explain the changes in serum proteins.

Another subject became nauseated and vomited during the injection of the contrast medium, and this was followed by tachycardia (130 beats/min), a small decrease in ceruloplasmin (from 0.26 to 0.18 g/l) and a minor fibrinolysis. However, a decrease in ceruloplasmin and fibrinolysis was also noted in another volunteer with no adverse reactions.

Patients with adverse reactions to contrast media have been reported to exhibit marked disturbances in sodium, calcium and especially potassium serum concentration which did not normalize within 24 hours (23). We did not observe such changes in the two subjects who became nauseated during the injection of ioxaglate.

Thus, 2 of the 9 subjects in our investigation became nauseated. The number of subjects is too few to draw any conclusion as regards the frequency of this type of side effect. The influence of the procedure itself cannot be excluded. Severe adverse reactions following intravenous injection of ioxaglate appear to be few, but the frequency of nausea and vomiting has been reported to correspond to that of conventional monoacidic ionic contrast media (5, 34). Several authors have tried to

explain the cause of the adverse reaction to contrast media (8, 20). Still no one has been able to show a direct correlation between changes in different parameters, such as release of histamine and serotonin, inhibition of cholinesterase, activation of coagulation and complement systems and clinical reactions (35).

Conclusion. No clinically significant changes following high dose intravenous injection of ioxaglate were found in biochemical parameters, the coagulation and fibrinolytic systems, fractionated plasma proteins, and in ECG and blood pressure.

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EFFECT OF IOXAGLATE ON THE LIVER AND PANCREAS FOLLOWING SELECTIVE VISCERAL ANGIOGRAPHY IN MAN

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Abstract

Selective visceral angiography was performed with the ionic, monoacidic, dimeric contrast medium ioxaglate (280 and 320 mg I/ml). Twenty patients with and without disease of the liver and/or pancreas were prospectively and consecutively studied. Changes in the serum activities of ALAT, ASAT, GT, AP, and pancreatic isoamylase and changes in the level of serum bilirubin, prothrombin index and haematocrit were evaluated sequentially before and after angiography. The total volume of contrast medium ranged from 100 to 340 ml per patient and the median dosage was 3.5 ml per kg body weight. There was no statistically significant elevation within the entire group of patients in the measured parameters after angiography when compared with pre-angiographic values. No clinically important toxic effect on the liver or pancreas induced by the contrast medium was found.

A large number of chemical substances may produce hepatic injury. Adverse effects on the liver induced by drugs are relatively uncommon. When they occur, they are usually induced by therapeutic drugs, seldom by diagnostic drugs (29).

Previous experimental and clinical investigations indicate that selective visceral angiography with common monomeric ionic tri-iodinated contrast media, such as diatrizoate, metrizoate and iothalamate, is a safe method for diagnosing abdominal disease. In several investigations no or only a small, but statistically significant, increase in serum activity of liver enzymes has been reported after selective visceral arterial injections in animals (8, 12, 17, 18, 26) and in man (2, 9, 12, 13).

The ionic contrast media commonly used today

have, however, disadvantages when injected into vessels mainly due to their hypertonicity relative to blood (3, 4, 6, 19, 22, 25). To obtain a contrast medium with an osmolality closer to that of blood, both non-ionic monomeric and ionic dimeric compounds have been synthesized. The low osmolality non-ionic monomers metrizamide, iohexol, and iopamidol and the ionic dimer ioxaglate have thus been proved to have lower acute general intravenous toxicity and to induce fewer side-effects than the commonly used ionic monomeric contrast media (3, 4, 6, 11, 19, 21–23).

Selective visceral angiography with metrizamide and iohexol produced minimal toxic effects on the liver in animals (16, 26) and in man (27) and with metrizamide no toxic effects were shown on the pancreas in man (27). The possible toxic effects induced by ioxaglate in selective visceral angiography have not been investigated in animals or in man.

Hence, the aim of the present investigation was to determine the effects of selective visceral angiography with ioxaglate on the liver and pancreas by studying enzymes in patients with or without hepatic and/or pancreatic disease.

Material and Methods

Twenty patients referred for selective visceral angiography (9 females and 11 males, median age 61

years, range 20–83 years) were prospectively and consecutively studied.

Fourteen of these 20 patients had carcinoma of either the liver, colon, pancreas, common bile duct, kidney or leiomyosarcoma. Five of these 14 patients had liver involvement of the carcinoma. Other diagnoses were pheochromocytoma, intrahepatic artery aneurysm, fistula between gall-bladder and colon, and cirrhosis of the liver.

Fifteen of the 20 patients were operated upon before or after angiography (median 5 days after angiography, range 6 days before to 14 days after). Six patients underwent nephrectomy, one adrenalectomy, 3 Whipple's operation, and 5 surgery on the bile ducts in combination with surgery on the small or the large bowel.

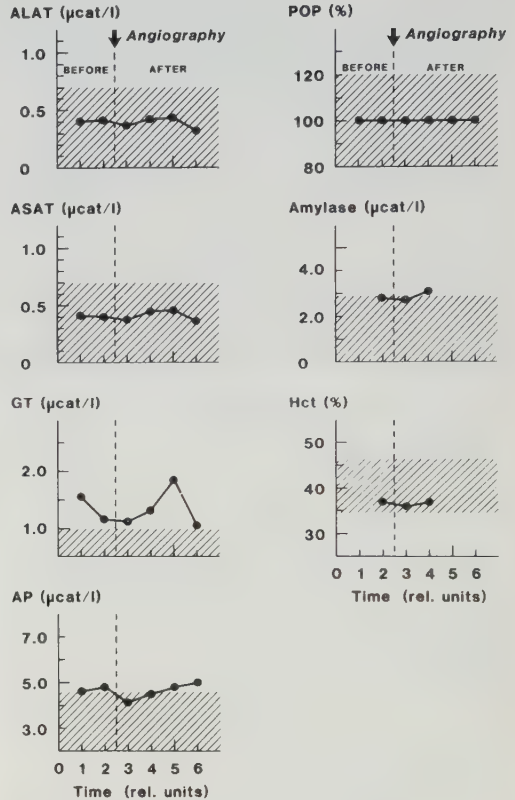
Fifteen patients were medicated with 1 to 7 different drugs mainly for heart failure or hypertension, but some received antibiotics and/or cortisone. One patient also received cytotoxic drugs on day 14 after angiography.

Angiography and contrast medium. The patients were premedicated with a 10 mg diazepam suppository administered 30 min before the examination. Local anaesthesia with mepivacaine (Carbocain) was given at the puncture site around the femoral artery.

Celiac, hepatic, superior and inferior mesenteric and renal angiographies were performed percutaneously with polyethylene catheters (OD/ID 2.2/1.45 mm). The ionic monoacidic dimeric ioxaglate (Hexabrix, Laboratoire Guerbet, Aulnay-sous-Bois, France), 280 or 320 mg I/ml in 9 and 11 patients, respectively, was used as the contrast medium (median total dose 250 ml, range 100–340 ml, median dose/kg body weight 3.5 ml, range 1.3–5.8 ml). Thirty to 50 ml contrast medium was injected with an automatic pressure injector (Medrad, Mark IV) into the celiac artery, 30 to 40 ml into the hepatic artery, 40 to 50 ml into the superior mesenteric artery and 15 to 25 ml into the inferior mesenteric artery. The injection rate was 6 to 20 ml/s. Five of the injections into the superior mesenteric artery were given after intraarterial administration of 9 µg bradykinin and one injection after administering 40 mg papaverine; moreover, in this latter patient 2.5 µg angiotensin was given before one contrast medium injection into the hepatic artery.

Fifteen patients received 2 or more selective visceral injections (median 3.5, range 1–6 injections).

Other diagnostic procedures. Five patients under-



Alterations in the median values of the serum activities of ALAT, ASAT, GT, AP, and prothrombin index (%) pancreatic isoamylase (µcat/l), and haematocrit (%) during the observation period. Normal limits for the measured parameters are indicated. Definition of time 1 = days 1–14 before, 2 = immediately before, 3 = immediately after, 4 = day 1 after, 5 = days 2–14 after, and 6 = days 15–46 after angiography.

went urography before or after angiography (median 8 days before, range 21 days before to 19 days after). Seven patients were examined with endoscopic retrograde cholangiopancreatography (ERCP) during the observation period (median 7 days before angiography, range 14 days before to 18 days after). Thirteen patients were examined with computed tomography (median 2 days before, range 19 days before to 12 days after angiography). In these investigations metrizoate (Isopaque, Nyegaard & Co., Oslo, Norway) was used as contrast medium.

Sampling and analysis. Changes in the activities of liver and pancreatic serum enzymes, bilirubin, prothrombin index, and haematocrit were studied

Table 1

Serum activities (median and range) of ALAT and ASAT and the haematocrit values before and after selective visceral angiography with ioxaglate.

	No. of patients	Serum activities ($\mu\text{cat/l}$)					
		ALAT		ASAT		Hct (%)	
		Median	Range	Median	Range	Median	Range
Before angiography							
1-14 days	17	0.40	0.15-4.20	0.41	0.24-2.48		
Immediately	20	0.41	0.13-3.79	0.40	0.23-2.70	37	30-43
After angiography							
Immediately	20	0.37	0.11-3.58*	0.37	0.19-2.34*	36	23-41*
Day 1	17	0.42	0.11-4.25	0.42	0.15-2.43	37	32-42
2-14 days	13	0.43	0.19-0.87	0.43	0.25-0.89		
14-46 days	10	0.32	0.15-0.81	0.32	0.27-1.96		
Normal reference range		<0.67		<0.67		35-48	

* Significant decrease compared with the pre-angiographic values, $p < 0.05$.

sequentially 1-2 weeks before to 6 weeks after angiography.

Venous blood was obtained 1-14 days before, the first day, 2-14, and 15-46 days after angiography. Arterial blood was taken from the catheter immediately before and after angiography.

All samples were continuously analysed at the Department of Clinical Chemistry, Malmö General Hospital according to procedures previously described (10, 20, 24, 28).

For the statistical analyses the Wilcoxon signed rank test for paired differences was used. p -values less than 0.05 were considered to be significant.

Results

Statistical evaluation. Following selective visceral angiography with ioxaglate, no significant elevation occurred in the activities of liver and pancreatic serum enzymes, bilirubin, or prothrombin index ($p > 0.05$) within the entire group of patients. There was a small, but significant, decrease ($p < 0.05$) in the measured parameters except prothrombin index immediately after angiography when compared with the values obtained before angiography.

Ten patients had no or one abnormal value of the measured parameters before angiography, whereas the remaining 10 patients had 2 or more elevated values. There was no statistically significant elevation in the measured parameters within these 2 subgroups of 10 patients.

Parameters measured. Alterations of the median values of the activity of liver and pancreatic serum enzyme, prothrombin index and haematocrit in the entire group of patients during the observation period are shown in the Figure. The median values and range are summarized in Tables 1 and 2. A level of prothrombin index exceeding 100 per cent is given as 100 per cent in the results. The pre-angiographic level of pancreatic isoenzyme was elevated in 9 patients. Seventeen patients had normal bilirubin values throughout the observation period. Two patients with carcinoma of the common bile duct and one with fistula between the gall-bladder and colon had elevated pre- and postangiographic bilirubin values.

Normal and decreased values. There was no elevation in the measured parameters in 14 of the 20 patients. Except for the small decrease in the measured parameters immediately after angiography, a decrease in one or several of the measured enzyme activities was found in 7 of these 14 patients during the observation period.

Increased values. In the remaining 6 patients, an increase was recorded in some parameters, and these patients are presented below. The first value within the parentheses is the value obtained immediately before angiography.

One patient displayed a slight increase in the GT (1.09-1.45 $\mu\text{cat/l}$) and AP (5.9-7.4 $\mu\text{cat/l}$) serum activities during weeks 2-4 after angiography.

Another patient reacted with a slight increase in

Table 2

Serum activities (median and range) of AP, GT and pancreatic isoamylase before and after selective visceral angiography with ioxaglate

	No. of patients	Serum activities ($\mu\text{cat/l}$)					
		AP		GT		Isoamylase	
		Median	Range	Median	Range	Median	Range
Before angiography							
1-14 days	17	4.6	2.3-24.0	1.55	0.32-19.8		
Immediately	20	4.8	2.1-22.8	1.15	0.32-20.8	2.8	0.8-103
After angiography							
Immediately	20	4.1	2.1-23.2*	1.13	0.30-20.2*	2.7	0.8-94*
Day 1	17	4.5	2.3-26.0	1.28	0.28-20.5	3.1	0.5-44
2-14 days	13	4.8	2.2-19.8	1.84	0.72-6.3		
15-46 days	10	5.0	2.6-22.0	1.06	0.78-10.1		
Normal reference range		<4.6		<1.0		<2.9	

* Significant decrease compared with the pre-angiographic values, $p < 0.05$.

the GT (0.47-0.92 $\mu\text{cat/l}$), ALAT (0.56-0.86 $\mu\text{cat/l}$), and ASAT (0.62-0.73 $\mu\text{cat/l}$) serum activities but without any increase in the AP level one week after angiography. Three months later this patient developed a non-A, non-B hepatitis and a few months later a carcinoma of the colon was detected.

A third patient reacted with a moderate increase in the serum activities of GT (0.87-5.5 $\mu\text{cat/l}$), AP (2.6-5.5 $\mu\text{cat/l}$), and a slight increase in the ASAT (0.26-0.89 $\mu\text{cat/l}$) and ALAT (0.20-0.79 $\mu\text{cat/l}$) serum activities during week 2 after angiography. Whipple's operation had been performed one week before these samples were obtained.

Two patients had carcinoma affecting the common bile duct and they reacted with a slight increase in the AP value (22.4-31.0 and 22.7-26.0 $\mu\text{cat/l}$ respectively) the first day after angiography but had no elevations in the GT, ASAT, and ALAT levels.

The sixth patient had a transient increase in the GT (6.6-7.4 $\mu\text{cat/l}$) and AP (15.6-17.8 $\mu\text{cat/l}$) levels on the first day and one week after angiography.

Other effects. No adverse effects such as urticaria, nausea, vomiting, or the like were observed in any of the 20 patients.

Discussion

The method of choice for detecting early toxic effects of drugs on the liver is to study the serum activity of liver enzymes. An elevated serum pan-

creatic isoamylase level indicates pancreatic damage, but it is less correlated with the degree of injury as compared with the elevated serum transaminases due to liver injury (1, 25).

An acute drug-induced injury of the liver usually produces a continuous elevation in the serum transaminase levels and AP during the first day, with a peak after 24 to 30 hours. This elevation is followed by a rapid decrease in the liver enzyme levels, reaching the lowest values within 1 to 5 days after the acute intoxication (5, 30).

We considered the observation period in our investigation sufficient to detect acute and subacute toxic effects of the injected contrast medium. It was not possible to follow all the patients for 6 weeks after angiography principally because of the nature of their disease and the discharge of some patients from hospital.

There is no difference at any time between venous and arterial serum enzyme activities of simultaneously obtained samples (5). Therefore, in our investigation, the venous pre- and postangiographic values have been compared with the arterial samples obtained immediately before angiography.

Within the entire group of 20 patients, there was no significant increase in the measured parameters during the observation period. Thus, no strong toxic effects on the liver or pancreas can be ascribed to the contrast medium ioxaglate.

In 7 patients one or more of the measured enzyme

activities were decreased during the observation period, reflecting a regression of the patients' disease.

Six patients reacted with a slight increase in some of the measured liver enzymes. In 3 of these patients there was no increased activity immediately after or during the first week after angiography. The increase appeared in 2 of these 3 patients during week 2 or later and in the remaining patient after surgery. If there was any induced injury to the liver or pancreatic cells during angiography, an elevation of the liver enzymes most likely should have occurred within the first 24 hours (5, 30). Thus, the changes in liver enzymes in these 3 patients are probably attributable to other factors, such as the disease itself or the surgery.

Two of the remaining 3 patients had a carcinoma of the common bile duct, and the last patient had cirrhosis of the liver and gall-stones reflected by continuously increasing serum GT and AP values before angiography. Thus, we assume that the small increase in these parameters observed the first day after angiography were part of a continuous increase due to the patient's disease. The serum activity of GT and AP rapidly decreased in the 2 patients with carcinoma of the common bile duct after internal drainage of the bile.

In samples obtained immediately after angiography we found a statistically significant simultaneous decrease in enzyme serum activity and haematocrit. This accords with previous investigations and is probably a result of the haemodilution induced by the hypertonicity of the contrast medium (7, 19).

In animals most of the experimental investigations have revealed a small, but statistically significant, increase in the activities of liver enzymes (8, 12, 16, 26), whereas only a few investigations have shown no statistically significant elevation (17, 18).

In man the experience is just the opposite and in most of the investigations there has not been any statistically significant elevation of the liver enzyme activities (9, 12, 13, 27); only one investigation (2) has shown a statistically significant alteration in the serum activity of GT, but not in ALAT and ASAT.

This discrepancy in results between animals and man can, to some extent, be explained by the much larger single doses per kg body weight used in the animal experiments, although the total dose injected per kg body weight has been within the same limits. Also, in these studies where an increase of serum enzyme activity was found, the degree of injury to

the liver has been considered to be small and transient and probably without any clinical importance.

ALMÉN (2) using conventional ionic contrast media found a statistically significant elevation of GT in 7 of 10 patients with malignant tumours of the liver. It has been shown that the GT and AP enzymes (membrane enzymes) appear in increased concentration in hepatic tumours (14, 15). Thus, the increased serum GT activities found by ALMÉN (2) does not necessarily mean that the contrast medium was hepatotoxic. It could imply that the contrast medium released GT enzymes surrounding the tumours, as there was no simultaneous elevation in serum activities of ALAT and ASAT (cytosol and mitochondrial enzymes), which better reflect hepatocellular injury. In our investigation, 2 patients of 5 with a liver tumour or metastases had a slight elevation of GT and AP the first day after angiography. The number of patients was too small to be able to confirm the findings of ALMÉN (2). Further in his study more selective injections in the hepatic artery were used than in our investigation.

Injection of a contrast medium into the visceral arteries in patients with impaired liver function has been shown to be relatively safe (9, 12, 13). Our results support this, as there were 10 patients with at least 2 or more abnormal pre-angiographic serum enzyme levels and 15 patients who were operated upon during the observation period without any statistically significant difference in the parameters measured within these groups.

Experimental research has revealed that injection of contrast media in combination with occlusion of the visceral arteries by the balloon technique in pigs (16) or by clamping the aorta above and below the celiac trunk in dogs (12) only results in a slight, transient increase in serum activity of liver enzymes which is probably due to the occlusion in combination with a large amount of contrast medium.

Our results with ioxaglate in selective visceral angiography support the main conclusion in previous experimental and clinical investigations that selective visceral angiography with modern contrast media is a safe method for diagnosing abdominal disease, both in patients with and without impaired liver and/or pancreatic function and in conjunction with other diagnostic procedures and surgery.

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**DEMONSTRATION of the RENAL VENOUS SYSTEM
at ROUTINE RENAL ARTERIOGRAPHY**

A comparison between metrizoate, metrizamide and ioxaglate

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ABSTRACT

The demonstration of renal veins during routine renal arteriography was retrospectively investigated and blindly scored in 60 patients. Three different types of contrast media were used: one high-osmolar ionic monomeric (metrizoate) and two low-osmolar, the non-ionic monomeric (metrizamide) and the ionic monoacidic dimeric (ioxaglate). The renal veins and the inferior vena cava were significantly better and more often demonstrated when ioxaglate was used compared with metrizoate and metrizamide. There was no significant difference between metrizoate and metrizamide. Following semiselective renal artery injection, the main renal veins were demonstrated with a diagnostically acceptable quality with ioxaglate in 76%, with metrizamide in 40% and with metrizoate in 29%. On selective renal artery injection the demonstration of renal veins increased to 85% with ioxaglate and remained unchanged with metrizamide (38%) and metrizoate (26%).

Semiselective or selective renal arteriography with ioxaglate at an ordinary dose was in most patients sufficient to allow evaluation of renal vein involvement in disease, rendering high dose selective renal arteriography or selective renal phlebography unnecessary.

A slower diffusion rate of ioxaglate compared with metrizoate and metrizamide is considered to be the major explanation for the better demonstration of the renal veins.

INTRODUCTION

Routine renal arteriography performed with currently used contrast media is often insufficient to allow detailed anatomical evaluation of the renal veins (1,4, 9,27), which is important in many situations, e.g., evaluation of renal carcinoma and renal vein thrombosis, selection of kidney transplant donors, and sampling of renal veins (3). The method used today for analysing renal vein morphology is selective retrograde phlebography (15,33) often combined with injection of epinephrine into the renal artery (27), or by transient balloon occlusion of the corresponding renal artery or the aorta above the renal arteries (11,13,26,33).

The demonstration of renal veins during selective renal arteriography has been improved in experimental investigations in animals using non-ultrafiltrable contrast agents (8,34), but clinical application has not been possible because of the high toxicity of these contrast media.

Some authors have suggested continuous injection of large doses of contrast media (50 ml) into the renal artery supplying a renal carcinoma if the kidney should be removed after the investigation (14).

During the last few years new angiographic contrast media with low toxicities have been developed. Hence, our aim was to compare the ability of these new contrast media to demonstrate the renal veins during renal angiography. The following contrast media were investigated: the ionic monoacidic monomeric metrizoate (Isopaque Cerebral, Nyco, Oslo, Norway), the non-ionic metrizamide (Amipaque, Nyco, Oslo, Norway) and the ionic monoacidic dimeric ioxaglate (Hexabrix, Guerbet, Aulnay-sous-Bois Cedex, France).

MATERIAL and METHODS

The appearance of the renal vein system during routine renal arteriography was retrospectively studied in 60 patients. The contrast medium concentration was 280 mg I/ml in all the investigations. Twenty-eight patients (median age 63, range 29-76 years) received metrizoate, 15 (median age 63, range 20-79 years) metrizamide and 17 (median age 58, range 32-83 years) ioxaglate. Fifty-five patients had normal plasma creatinine levels (upper normal limit 115 $\mu\text{mol/l}$ for men and 100 $\mu\text{mol/l}$ for women). In 3 of the patients receiving metrizoate and in 2 receiving metrizamide, the creatinine value was slightly elevated (105, 114, 151, 112, 152 $\mu\text{mol/l}$, respectively). Fig. 1 shows the chemical structure and Table 1 the physical and chemical data of the investigated contrast media. Each patient in the series received only one contrast medium.

Angiography Polyethylene catheters (OD/ID 2.2/1.45 mm) were used and the contrast medium was injected by an automatic pressure injector (Medrad, Mark IV). The first injection was always

a lumbar aortography, semiselective technique (5), and was usually followed by one or several renal artery injections. The angiographic procedures were the same for all the patients. The film series comprised 12 films taken during the first 12 seconds immediately after starting the injection.

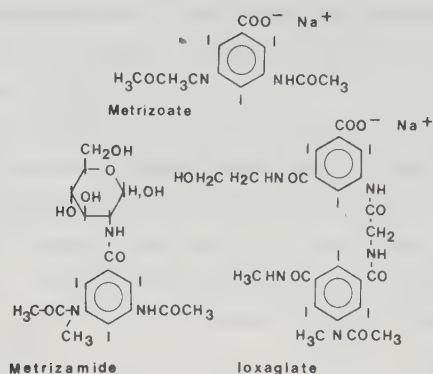


Fig 1 Chemical structure of the investigated contrast media

Table 1

CONTRAST MEDIUM	METRIZOATE	METRIZAMIDE	IOXAGLATE
TRADE NAME	Isopaque	Amipaque	Hexabrix
IODINE CONTENT mg/ml	280	280	280
SUBSTANCE CONC. mol/l	0.73	0.74	0.37
OSMOLALITY mmol/kg water	1460	460	490
VISCOSITY 20°C mPa.s	7.2	9.7	8.7
37°C mPa.s	4.0	5.0	4.8
MOLECULAR WEIGHT	626	789	1258
CATION	Meglumine	---	Meglumine Sodium

Semiselective renal arteriography. Thirty millilitres of contrast medium (rate 20 ml/s) was injected through a catheter with 1 end hole and 6 side holes. The tip of the catheter was positioned in the renal artery supplying the normal kidney. With this technique it has been estimated that 5 ml of the totally injected 30/ml reaches the normal kidney (5).

Selective renal arteriography. From 8-15 ml (median dose 10 ml, rate 4-10 ml/s, median rate 8 ml) was injected through an end hole catheter with the tip placed in the renal artery.

High dose selective renal arteriography. In the patients in whom a tumour was found, an additional selective injection of 20-30 ml (median 25 ml, rate 8-10 ml/s, median rate 8 ml) was given into the artery supplying the tumour.

Scoring system The quality of demonstration of the renal veins on the angiograms was evaluated according to an arbitrary scoring system. The definitions of the scores are given in Table 2. To obtain a more consistent diagnostic approach, scores 0 and 1 were considered "not diagnostically acceptable" and scores 2 and 3 "diagnostically acceptable", thus insufficient or sufficient to allow evaluation of renal vein involvement in disease.

Antero-posterior films obtained of the renal veins were scored by two radiologists unaware of which contrast medium was used. Both the intrarenal (lobar and interlobar) and the main veins were scored. The demonstration of the inferior vena cava was scored when semiselective injections were given in the right kidney.

The number of injected kidneys in the different contrast media groups is presented in Table 3. When semiselective injections were performed, only the catheterized kidney was scored. The scores obtained during selective injection were compared with the previous semiselective injection concerning the same kidney.

Circulation time The time from the start of the injection to the first appearance and to the maximum of the contrast appearance of the renal veins was recorded.

Statistical analyses For the statistical analyses the Fisher exact test or the χ^2 -test was used. p-values less than 0.05 were considered to be significant. Significant corresponds in this paper to statistically significant.

Table 2

Score	Definition
0	No demonstration
1	Poor demonstration, insufficient for adequate delineation
2	Good demonstration, sufficient for adequate delineation
3	Very good demonstration, high homogenous radiographic density

Table 3 Number of patients and of investigated kidneys in the different contrast media groups

CONTRAST MEDIUM	Total no. of patients	SEMISELECTIVE INJECTION		SELECTIVE INJECTION		HIGH DOSE INJECTION	
		No. of injected kidneys left	right	No. of injected kidneys left	right	No. of injected kidneys left	right
METRIZOATE	28	13	15	18	16	5	1
METRIZAMIDE	15	6	9	10	6	3	2
IOXAGLATE	17	9	8	3	4	3	3

RESULTS

There was no significant difference in the distribution of scores 0+1 and scores 2+3 between left and right kidney within the contrast media groups. The scores for the intrarenal veins and the main renal veins were calculated. There was no significant difference between the scores in the two groups, and therefore only the results of the main renal veins are presented.

Semiselective arterial injection

The kidney scored during the semiselective injection was normal in most patients, only a few had a mild nephrosclerosis or hydronephrosis. Thus, no patient with a renal carcinoma in the injected kidney was included in this group.

Main renal veins The distribution of the scores is illustrated in Fig. 2. The sum of scores 2+3 was significantly higher in the ioxaglate group (76%) than in the metrizoate (29%) and metrizamide (40%) groups. There was no significant difference between the latter two groups.

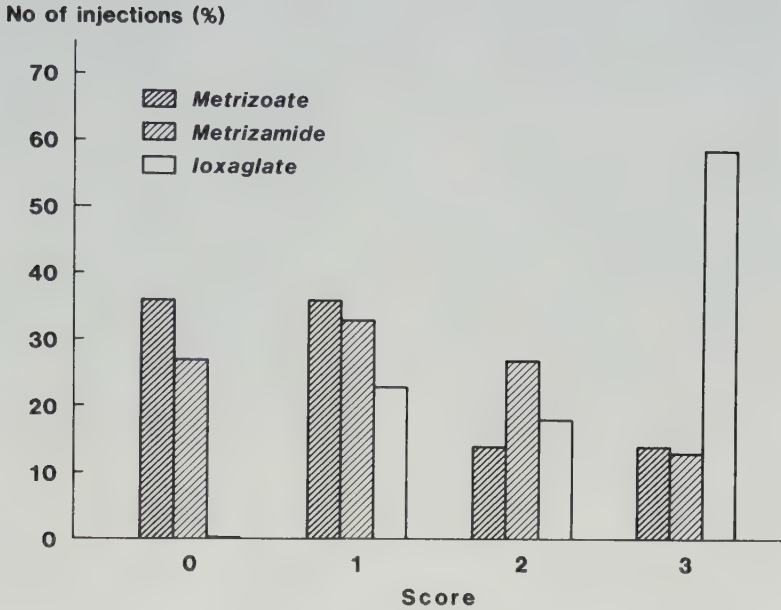


Fig 2 Distribution of the scores of the main renal veins during semiselective arterial injection

Inferior vena cava The inferior vena cava was demonstrated in 72 per cent of the patients when ioxaglate was used compared with 6 per cent for metrizoate and 0% for metrizamide following injection into the right renal artery.

Figs. 3 and 4 give examples of the renal veins during semiselective arterial injection with ioxaglate.

**Fig 3**

Arterial (a) and venous phase (b) during semiselective arterial injection with ioxaglate into the left kidney (dose 30 ml, rate 20 ml/s). About 5 ml of contrast medium goes to the semiselectively catheterized kidney with demonstration of the veins

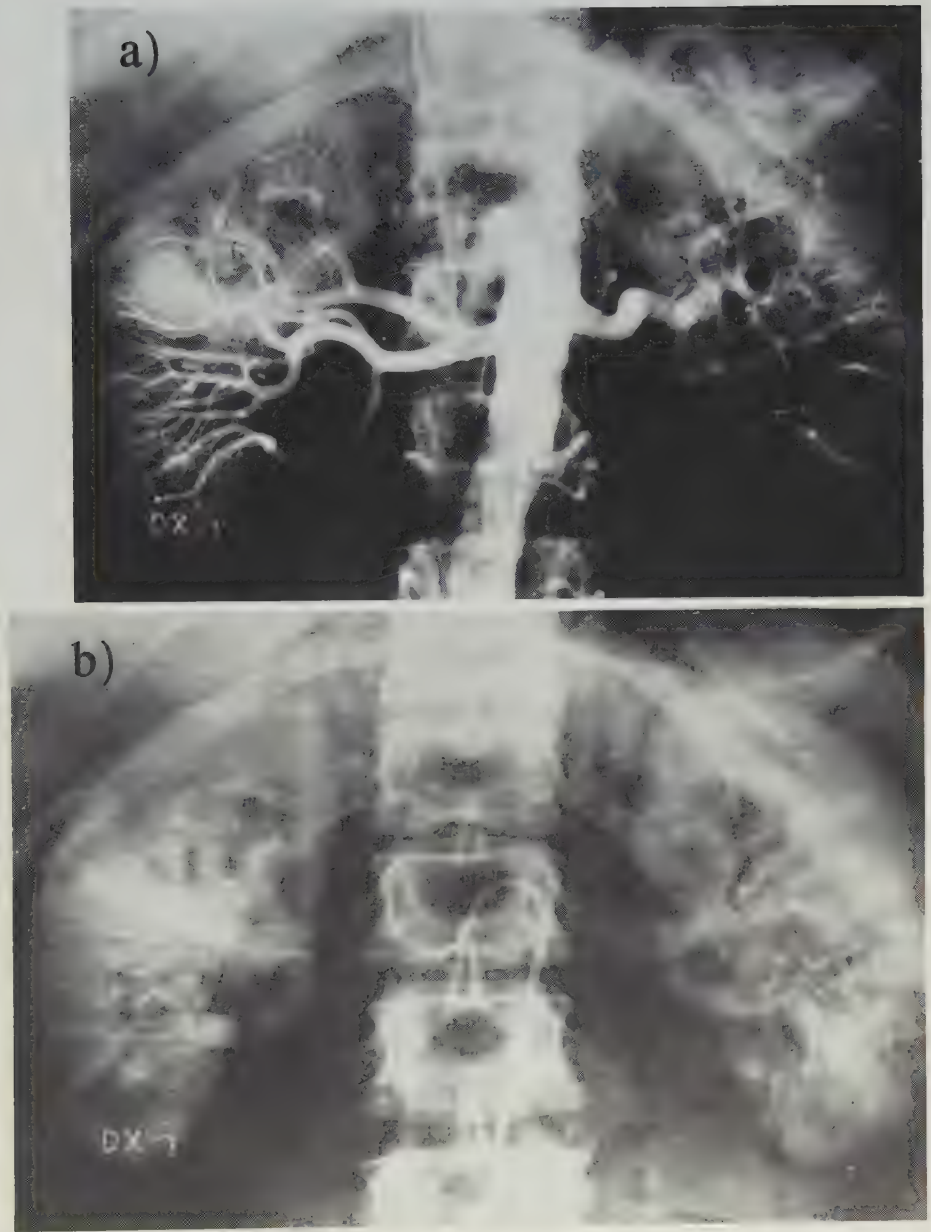


Fig 4 Arterial (a) and venous phase (b) phase during semiselective arterial injection with ioxaglate into the right kidney. The renal veins are demonstrated bilaterally

Selective arterial Injection

There was no essential difference in pathology, e.g., carcinoma, renal cyst, and renal calculi between the different contrast medium groups. There was no significant difference in the total amount of contrast media used or in the injection rate between the groups during the selective injections.

Main renal veins The distribution of the scores is presented in Fig. 5. The main renal veins could be demonstrated in a diagnostically acceptable way in the ioxaglate group significantly more often (85%) compared with metrizoate (26%) or metrizamide (38%). No significant difference was found between metrizoate and metrizamide.

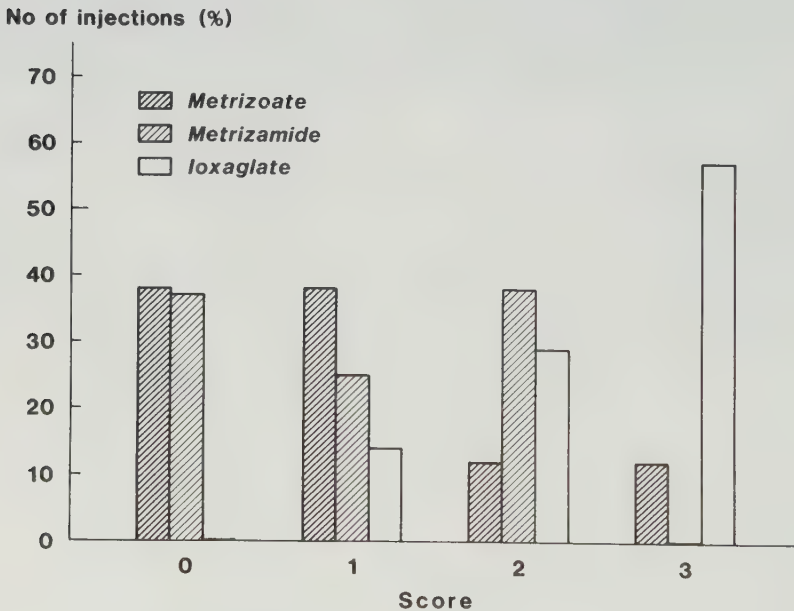


Fig 5 Distribution of the scores of the main renal veins during selective arterial injection

Selective versus semiselective arterial injection into the same kidney

There was no significant improvement of the opacification of the renal veins during selective injection compared with the previous semiselective injection into the same kidney within the metrizoate and the metrizamide groups. No correlation was found between the total amount injected or the injection rate of the contrast media and the obtained score. The number of observations in the ioxaglate group was too small to allow any statistical conclusion.

Selective high dose arterial injection

Patients in whom a high dose of contrast media was injected into the renal arteries supplying the tumour underwent a unilateral nephrectomy. The pathology report showed no tumour involvement of the renal veins in all but 2 patients (in the metrizamide group) who were excluded from the statistical evaluation.

Main renal veins The distribution of the scores is presented in Table 4. Administration of ioxaglate resulted in a significant higher frequency of diagnostically acceptable demonstration of the main veins (100%) compared with that of metrizoate (17%). The number of investigated kidneys in the metrizamide group was too small to allow a comparison. Fig. 6 demonstrates the renal arteries and veins following selective high dose injection of ioxaglate in a patient with a renal carcinoma.

Table 4

Score	Metrizoate	Metrizamide	Ioxaglate
0-1	5	1	0
2-3	1	2	6

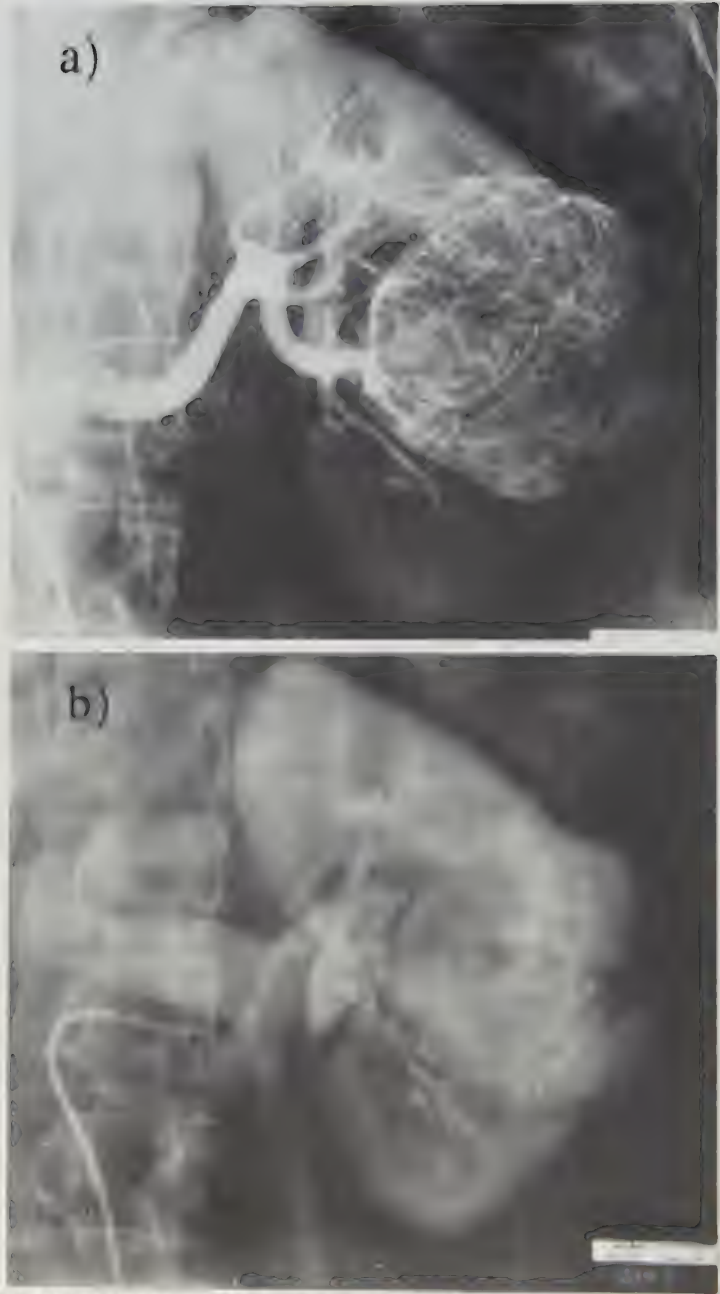


Fig 6 Arterial (a) and venous (b) phase during high dose selective arterial injection (dose 25 ml, rate 10 ml/s) with ioxaglate into the left renal artery in a patient with renal carcinoma. The main renal veins and left ovarian vein are demonstrated — these received score of 3

Circulation time

No difference was obtained between the different contrast medium groups during semiselective injection as regards the time of the first appearance of veins (median 5 s, range 3-10 s for intrarenal veins and median 6 s, range 3-10 s for the main veins) or the time for maximum opacification (median 10 s, range 6-12 s for intrarenal veins and median 11 s, range 8-12 s for the main veins). The corresponding values for the median times of the selective injections were 1-2 seconds shorter.

DISCUSSION

Using various arteriographic techniques, we have shown that ioxaglate, more often than metrizoate and metrizamide, demonstrates the renal veins. We also conclude that semiselective or selective renal artery injection with ioxaglate at an ordinary dose in most patients is sufficient to allow evaluation of renal vein involvement in disease, rendering high dose selective renal artery or vein injection unnecessary.

All three contrast media were injected into the renal artery at equal iodine concentration, and they all within 15 seconds reached their maximal concentration in the renal veins. The obtained better demonstration of the renal veins following injection of ioxaglate thus indicates a higher iodine concentration in the renal veins than after the injections of metrizoate and metrizamide.

Theoretically, the explanation to a difference in contrast medium concentration in the renal veins may be found among differences in the following properties of the various media:

I) effect on renal blood flow (RBF), II) filtration, III) dilution and IV) diffusion in the kidney.

I. Contrast medium effects on renal blood flow

Experimental investigation immediately following intraarterial injection have shown an early increase in blood flow that was viscosity-dependent (17,22) and that the ionic monomeric contrast medium induced the greatest increase in RBF (29,30). If an increase in RBF would result in a better demonstration of the renal veins metrizoate in our investigation should have best

demonstrated the renal veins. Our results, however, showed the opposite and moreover the differences in viscosity of the investigated contrast media are small (Table 1). We assume that effects of contrast medium on RBF probably will not explain the difference in renal vein demonstration.

II. Filtration of contrast medium in glomerular and postglomerular renal capillaries

A decrease in glomerular filtration rate (GFR), filtration fraction (FF) and postglomerular filtration results in a higher venous concentration of an injected substance. Some investigators have found a decrease in GFR and FF following injection with hypertonic ionic contrast medium (12,18,35) with a maximum at 30 s or later after the start of injection and these effects being more pronounced after high osmolality media than after low osmolality agents (36). However, there are no experiments indicating any decrease in GFR and FF during the first 15 seconds following renal arterial injection. Moreover, if nevertheless such effects influenced our results, this would be in favour of the hyperosmolar metrizoate having the greatest effects on GFR and FF and thus would result in the best renal vein demonstration. Our results showed the opposite.

The postglomerular filtration pressure is much lower than the filtration pressure across other capillaries, e.g., in peripheral muscle (20) and the transcapillary velocity of molecules (smaller than inulin) depends more on the diffusion rate than the filtration rate (28). This means that the postglomerular loss of contrast molecules across the capillary walls due to filtration will be small. We thus consider that any possible differences between the investigated contrast media in glomerular and postglomerular filtration rate and the filtration fraction (FF) cannot account for the different concentration of the media in the renal veins.

III. Dilution of intravascular contrast solution

Experiments on peripheral muscle vessels indicate that the dilution of a compound on the venous side increases with increasing osmolality (20). Accordingly metrizoate would be more

diluted than ioxaglate and metrizoate. As the kidney, unlike other organs, possesses hypertonic tissue and plasma (31,32) and the osmolality of the peritubular tissue even may exceed that of the contrast medium solution (up to 2100 mmol/kg water) we assume that the difference in osmolality between different contrast media not is accompanied by a corresponding difference in dilution of the contrast medium in the renal veins. This is supported by an experimental study of Morris et coll. (23) who found no major difference in the degree of dilution between low and high osmolality compounds in the renal veins. The explanation may be that in the kidney the fluid volume, available to reduce the osmotic gradient induced by the contrast medium, is limited.

IV. Diffusion of contrast medium from renal vessels

Parameters determining differences in diffusion rate of contrast media are concentration gradient, viscosity, molecular size and shape, electrical charge, and degree of lipophilicity (2,20).

The initial concentration gradient of ioxaglate is lower than that of metrizoate and metrizamide since it contains only half the number of iodine-carrying molecules at equal iodine concentration (Table 1, Substance conc.). Accordingly, ioxaglate initially has a lower diffusion rate compared with metrizoate and metrizamide.

The viscosity of a solution affects the diffusion rate of the molecules. Since there are no major differences in viscosity between the three contrast media utilized in our investigation, we do not believe that a difference in viscosity is a major factor to account for the assumed difference in diffusion rate. There is ample experimental support of the idea that the kidney is adapted to high viscosity in the postglomerular vessels (31). The viscosity probably exceeds that of the three contrast media in our investigation. Thus, the contrast medium solute will add very little to the already high effective viscosity in this part of the kidney.

The diffusion rate of molecules across capillary membranes is inversely correlated with molecular weight and size (20,28). The dimer ioxaglate is a heavier and larger molecule than both

metrizoate and metrizamide and consequently has the lowest diffusion rate.

Biological membranes have a greater permeability to the non-ionized, than the ionized fraction of weak acids and bases (21). Because of possible repelling forces against the negatively charged metrizoate and ioxaglate at the membrane pores and the larger non-ionized fraction and also a greater lipophilicity of metrizamide (24), it might be assumed that metrizamide will penetrate the capillary faster than the other two contrast media. Our work indicates, however, that iodine concentration in the renal veins is higher for ioxaglate than for metrizoate and metrizamide. Consequently, we consider the differences between these contrast media in electrical charge or degree of lipophilicity of minor importance in explaining our results.

Contrast media are mostly characterized by their osmolality or viscosity and whether they are ionic or non-ionic. Little attention has been paid to differences in diffusion rate between various contrast media. Some investigators have found time-dependent differences in the distribution volume in the body and differences in normal and diseased organs (7,19). Other investigators have found or suggested the presence of differences in the diffusion rate between various contrast media (16,23), and ionic dimeric compounds seem to have the lowest diffusion rate. The diffusion rate of a contrast medium across a capillary membrane may have diagnostic implication, as shown in our investigation.

At an early presentation of the preliminary results of the present investigation (25), we thought that they may have important applications in contrast enhanced CT and intravenous digital subtraction angiography (DSA). However, later investigations have demonstrated that following intravenous injection the diffusion rate and distribution volume of mono- and dimeric contrast media are of only minor importance for the peak concentration in the great arteries (6). Our results seem to be exclusively valid for the kidney and can probably not be applied to other organs because the kidney is the only body organ adapted to high viscosity and high osmolality of solutes.

If we apply the work of Pappenheimer et coll. (28) to contrast medium, it is inferred that a contrast medium with the molecular size of inulin might be of great interest for CT and DSA, as the diffusion rate will be much slower compared to the current modern contrast media and still such a contrast medium will be freely filtered in the glomerular capillaries.

General conclusion

The hypothesis is advanced that the better demonstration of the renal veins with ioxaglate compared with metrizoate and metrizamide following intraarterial injection is explained by a slower diffusion rate across the capillary walls resulting in a smaller loss per unit time of the iodine-carrying molecules in the renal peritubular capillaries. Differences in concentration gradient, molecular weight, size and shape of the molecules and electrical charge may be the major factors explaining this hypothesized decreased diffusion rate of ioxaglate. The diffusion rate factors may predominate because the kidney is adapted to high osmolality and viscosity of solutes.

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**AORTOCERVICAL ANGIOGRAPHY with HIGH and LOW
OSMOLALITY IONIC CONTRAST MEDIA**

A clinical investigation of metrizoate and ioxaglate

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ABSTRACT

The influence of aortic arch injection of metrizoate 280 and 370 mg I/ml and ioxaglate 280 and 320 mg I/ml on EEG, heart rate, blood pressure, subjective responses, occurrence of involuntary movements and resulting image quality was investigated in 31 patients. Ioxaglate 320 produced less haemodynamic changes and subjective responses and as good image quality as the hyperosmolar contrast medium metrizoate 370 if subtraction procedure was used. Small and brief EEG changes were recorded in 9 out of 14 patients. Only metrizoate 280 induced significant bradycardia. Involuntary movements on the film with the best demonstration of the vessels occurred with no differences between the contrast media. There was no correlation between involuntary movements and image quality. Our investigation indicates that an ionic contrast medium which is intended for aortocervical angiography should have a concentration of at least 320 mg I/ml, high viscosity, low osmolality and be no pure meglumine salt.

INTRODUCTION

Intravascular injection of high osmolality ionic monomeric contrast media (diatrizoate, metrizoate, iothalamate) may induce marked haemodynamic changes. These media have for example in angiocardiology and selective cerebral angiography been reported to cause both tachycardia, bradycardia and hypotension (10,17,22,26,40,41).

Because of the unfavourable effects of these contrast media, new media with an osmolality closer to that of plasma have been developed e.g. the non-ionic monomeric metrizamide, iohexol and iopamidol and the ionic dimeric ioxaglate. These media induce fewer haemodynamic effects in both angiocardiology, selective cerebral angiography and peripheral angiography (18,28,29,36,39) and have lower acute general toxicity than the high osmolality ionic monomeric media (4).

There are few clinical investigations on the effects of contrast media injected into the aortic arch or root on either the heart (8,9,11,12,19) or the brain (22). Little attention has also been directed to the combined simultaneous effect on the brain and heart in aortocervical angiography.

The aim of our investigation was to evaluate whether the combined effect was less prominent when a low osmolality medium (ioxaglate) was used instead of a high osmolality medium (metrizoate). Changes in EEG, haemodynamics, subjective responses, involuntary movements and image quality were registered.

MATERIAL and METHODS

Thirty-one patients referred for aortocervical angiography were divided into 2 groups. EEG was recorded in group 1 only, whereas all other parameters were recorded in both groups. The cause of the investigation was explained to the patient and all gave their consent.

Contrast medium and injection order/Table 1/

Group 1 In 16 patients (median age 61 years, range 50-75 years) the first and second injections were administered randomly in a double-blind fashion with metrizoate 280 (280 mg I/ml, Nyco, Oslo, Norway) or ioxaglate 280 (280 mg I/ml, Guerbet, Aulnay-sous-Bois Cedex, France). Ioxaglate 280 was obtained by diluting ioxaglate 320 (320 mg I/ml) with sterile water.

Group 2 In 15 additional patients (median age 61 years, range 39-80 years) the investigated contrast media were metrizoate 370 (370 mg I/ml) or ioxaglate 320 injected randomly.

The third injection in both groups was with ioxaglate 320. The first and second injections of ioxaglate in group 2 are described as ioxaglate 320 (I) and ioxaglate 320 (II).

Angiographic technique A pig tail catheter (12 side holes, OD/ID 2.36/1.57 mm) was advanced via a femoral artery to the aortic arch about 8 cm above the aortic valve just proximal to the origin of the great vessels and remained there during the entire investigation. Each contrast medium injection (50 ml,-

rate 30 ml/s) was administered with an automatic pressure injector at room temperature and at an interval of 10-15 min.

Film series The angiography series began with two identical lateral projections of the neck at the level of the carotid bifurcation; the only difference was the change of the contrast medium. The third series was a lateral projection with a different angulation. The film series comprised 2 films per second for 5 s.

Table 1

Physico-chemical data of the contrast media used

GENERIC NAME TRADE NAME	METRIZOATE		IOXAGLATE		Human serum and plasma
	Isopaque Cerebral	Isopaque Coronar	Hexabrix 28 %	Hexabrix 32 %	
IODINE CONTENT mgI/ml	280	370	280	320	
OSMOLALITY mmol/kg water	1460	2150	480	590	290
VISCOSITY mPa.s	20°C	7.1	17.3	8.7	15.9
	37°C	4.0	8.4	4.8	7.5
CATIONS Sodium mmol/l	0	155	133	152	138-148
Meglumine	718	798	228	268	0
Calcium	4.3	4.3	0	0	2.2-2.6
NUMBER OF FIRST INJECTION	8	8	8	7	

Electroencephalography Routine EEG was recorded in 14 of the patients in group 1 by a 16 channel Elema-Schönander mingo-graph 1-10 days before, continuously during and 1-3 days after the angiographic procedure.

Haemodynamic assessment Heart rate was continuously recorded with precordial ECG from 1 min before to 5 min after the injections. The degree of bradycardia and tachycardia was expressed as the difference in time between the longest or shortest cardiac cycle before and after the injection (in hundredths of a second) as described previously (21). An increase or a decrease in length of the heart cycle of more than 0.04 s was considered bradycardia and tachycardia, respectively (21). Arterial blood pressure (BP) was manually recorded by cuff immediately before and after the injection, and sequentially 5 min after the injections. A change of 10 mm Hg or more from the

preinjection value was considered as an increase or decrease in blood pressure. The time of the first appearance, maximum radiographic density and disappearance of the contrast medium in the carotid bifurcation, intracerebral arteries and vertebral arteries was noted.

Subjective response The degree of heat and pain was assessed by the patient on a 100 mm visual analogue scale (38). On this scale the left end signified no heat or pain and the right end unbearable heat or pain.

Involuntary movements The degree of motion was graphically determined by comparing the original key angiogram (the film with the best demonstration of the vessels) with the first film, which was obtained simultaneously with the start of injection. The position of the hyoid bone in relation to the mandible and the hypopharyngeal air column was used as a landmark. A change of 1 mm or more was regarded as motion. Movements occurring during the first 2.5 s after the commencement of the injection were described as early movements and those occurring later than 2.5 s as late.

Image quality The degree of radiographic density and demarcation of the vessels of the carotid bifurcation on both the original key angiogram and the subtraction film was recorded by 2 radiologists according to an arbitrary scoring system (Table 2). Image quality was defined as the sum of these scores.

All assessed parameters were evaluated without knowledge of contrast medium or its concentration.

Statistical analyses The Wilcoxon's signed rank test and the Fisher exact test were used and p-values less than 0.05 were considered statistically significant.

Table 2 Definition of individual score

	Radiographic density	Demarkation
Not diagnostically acceptable	1 low	unsharp
	2 moderate	moderate sharp
Diagnostically acceptable	3 high	sharp
	4 very high	very sharp

Definition of sum of scores

Sum of scores	1-4	Not diagnostically acceptable image quality
(Image quality)	5	Boarderline image quality
	6-8	Diagnostically acceptable image quality

RESULTS

EEG There was no significant difference between the contrast solutions. Six patients had abnormal preangiographic EEGs. No significant changes were noted between EEGs obtained the days before and the days after angiography. Alterations appeared in the EEGs recorded in 9 out of 14 patients. In 6 of these patients a brief - 2-4 s - desynchronization, inhibition of alpha-activity was observed during and immediately after the injections of all the contrast media. In 2 of these 9 patients such desynchronization was observed at only one of the injections (ioxaglate 280, ioxaglate 320). In the remaining patient an increase in amplitude of the alpha-activity of the left centroparietal region was observed for 20 s following the first contrast medium injection (metrizoate 280); no change was noted after ioxaglate 280; and after ioxaglate 320 only a slight desynchronization lasting 3 s was noted.

Haemodynamic effects /Fig 1/

The number of patients with bradycardia was significantly higher following the injections of metrizoate 280 than after the other contrast media (Table 3). The median time of maximal bradycardia was 3 s and of the duration 5.5 s. Tachycardia was seen following all contrast media injections (Table 3). Hypotension was seen in 16-40% of the patients after the ioxaglate solutions

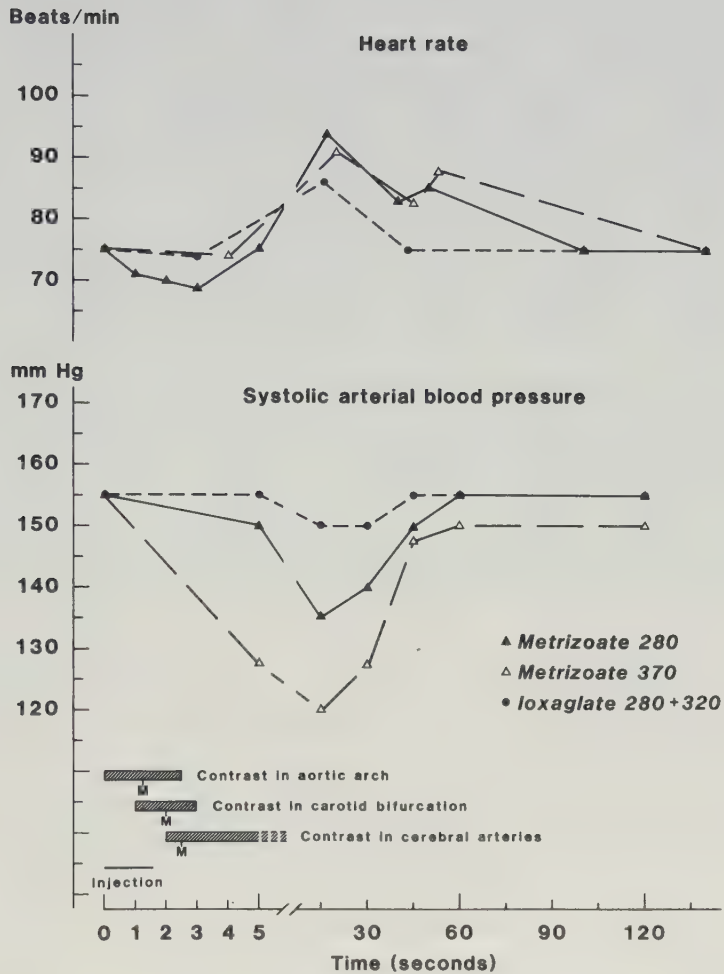


Fig 1

Time-related changes in heart rate and systolic arterial blood pressure (median values) following contrast medium injection into the aortic arch.

M = median time for maximum radiographic density in the vessels

and in all patients following injection of the metrizoate solutions (Table 3). The duration and the degree of the tachycardia and hypotension was significantly less in both groups following the injection of ioxaglate than of metrizoate. The time for occurrence of maximum change in hemodynamics is given in Fig 1. No significant difference was found in haemodynamic effects between the two solutions of ioxaglate.

There was no significant difference in time of first appearance, maximum radiographic density or disappearance from the investigated vessels between the different contrast media.

Subjective response /Table 4/ All patients experienced a significantly smaller sensation of heat after injection of ioxaglate than after metrizoate. Fifteen out of 16 patients reported that ioxaglate 280 induced less heat sensation than ioxaglate 320. One of 31 patients expressed pain, less after ioxaglate 320 than after metrizoate 370.

Image quality

Group 1 /Fig 2/ The image quality was equal on the key angiograms with metrizoate 280, ioxaglate 280 and 320. On the subtraction films ioxaglate 320 produced significantly better image quality.

Group 2 /Fig 3/ The image quality on the key angiograms was significantly better for metrizoate 370 compared with ioxaglate 320 (I). No significant difference was found on the subtraction films between metrizoate 370, ioxaglate 320 (I) and ioxaglate 320 (II). The image quality on the subtraction films was for ioxaglate 320 (I) and (II) significantly better than on the key angiograms.

Influence of subtraction technique and involuntary movements on image quality

Group 1 The subtraction procedure increased the image quality for both ioxaglate 280 and metrizoate 280 in 11 out of 16 patients and for ioxaglate 320 in 9 out of 12 patients. The subtraction procedure failed to increase the image quality from not acceptable to diagnostically acceptable in 8 out of 32

Table 3

	CONTRAST MEDIUM				
	M 280	GROUP 1 I 280	I 320	GROUP 2 M 370	I 320
BRADYCARDIA					
Number of patients with bradycardia	12/14	4/14	1/13	2/10	1/10
Maximal prolongation of heart cycle (0.01 s)	6(0-23)	2(0-8)	2(0-7)	4(0-94)	2(0-6)
Duration of bradycardia (s)	5.5(1-16)	4(0-7)	2(0-5)	3(0-14)	3(0-7)
TACHYCARDIA					
Number of patients with tachycardia	13/14	11/14	10/13	10/10	7/10
Maximal increase in heart rate (beats/min)	15(8-24)	10(2-20)	9(0-15)	15(11-25)	8(2-18)
Duration of tachycardia (s)	85(21-330)	31(0-75)	28(0-277)	145(45-385)	24(0-52)
SYSTOLIC AORTIC BLOOD PRESSURE					
Number of patients with hypotension	16/16	3/16	3/13	10/10	4/10
Maximal decrease in blood pressure (mm Hg)	25(10-50)	5(0-15)	5(0-20)	45(10-65)	5(10-20)
Duration of hypotension (s)	30(15-300)	0(0-30)	0(0-60)	55(30-240)	0(0-15)

Median values (range) of the degree and the duration in bradycardia, tachycardia and hypotension after contrast medium injection into the aortic arch. M = metrizoate, I = ioxaglate, 280, 320 and 370 correspond to mg I/ml. Bradycardia expressed as the maximal prolongation of heart cycle in hundredths of a second

Table 4

CONTRAST MEDIUM	Visual analogue scale scores [*] HEAT (mm)	
	median	range
GROUP 1 (n=13)		
Metrizoate 28%	76	51 - 98
Ioxaglate 28%	17	6 - 50
Ioxaglate 32%	24	14 - 41
GROUP 2 (n=14)		
Metrizoate 37%	82	21 - 98
Ioxaglate 32%	23	6 - 89

^{*} maximum possible score = 100 mm

original key angiograms after injection of the two 280 solutions but there were no such failures after ioxaglate 320.

Group 2 The subtraction procedure increased the image quality for ioxaglate 320 (I) in 9 out of 14 patients but also decrease the quality in 1 patient. Failure to increase image quality from not acceptable to diagnostically acceptable was seen in 3 out of 14 angiograms. The corresponding figures for metrizoate 370 were increase in 5 out of 14 patients, decrease in 1 patient and failure in 1 patient.

The onset of the bradycardia may partly influence the image quality. Bradycardia starting early during the injection was associated with a lower frequency of diagnostically acceptable image quality on the key angiograms than bradycardia starting late during or immediately after the injection. Otherwise no correlation was found between the degree and duration of bradycardia, tachycardia, decrease in blood pressure, diagnosis and the image quality on the key angiograms.

Involuntary movements /Table 5/

Motion as defined above was seen on one or several films in a majority of the patients regardless of contrast medium. These involuntary movements were limited to elevation of the hyoid bone and changes in hypopharyngeal air column. There was no difference between the contrast media in frequency or degree of early involuntary movements (corresponding to the time for the films that best demonstrated the vessels). The late involuntary movements were both less pronounced and less frequent following the injections of the ioxaglate solutions than after the metrizoate solutions. There was no correlation between the degree of involuntary movement and the injection sequence. There was no correlation between involuntary movements and obtained image quality.

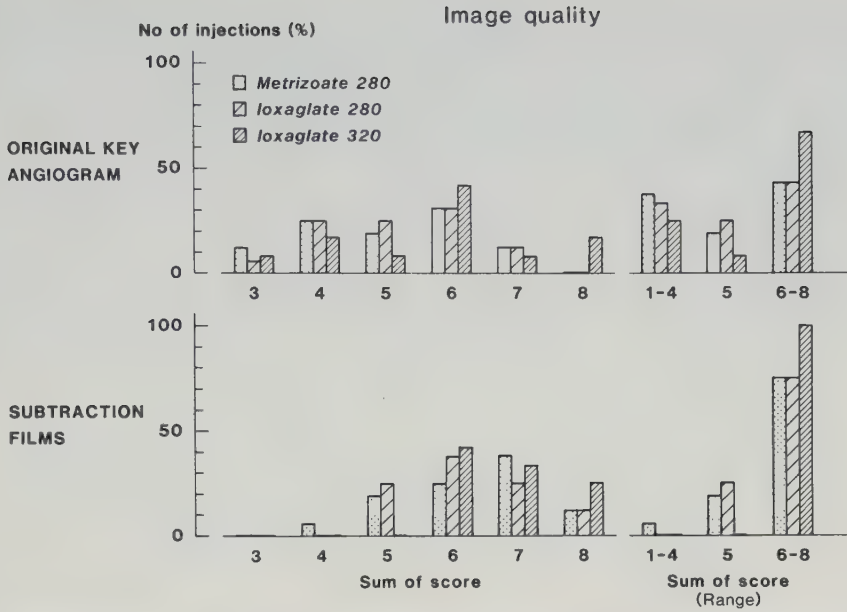


Fig 2

Distribution of the scores of image quality on original key angiogram and subtraction films in group 1. For definition of scores, see table 2

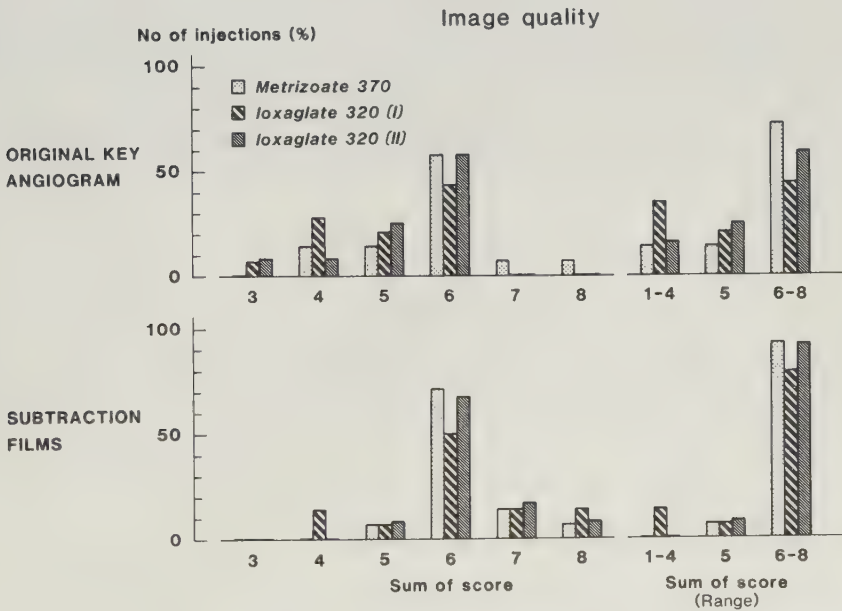


Fig 3

Distribution of the scores of image quality on original key angiograms and subtraction films in group 2

Table 5

Number of patients with MOVEMENTS during the
entire film serie original key angiogram

CONTRAST MEDIUM

GROUP 1

Metrizoate 28%	14/16	4/16
Ioxaglate 28%	10/16	4/16
Ioxaglate 32%	6/12	2/12

GROUP 2

Metrizoate 37%	12/14	6/14
Ioxaglate 32% (I)	9/14	4/14
Ioxaglate 32% (II)	8/12	2/12

Number of patient regardless of degree reacting with involuntary movements during the entire film series and at original key angiogram (best demonstration of the vessels) following contrast media injection into the aortic arch.

Other reactions No neurological symptoms were observed during the angiography or the day after. Following the injection of metrizoate 280, one patient became nauseated in connection with a decrease in BP. Following the injection of metrizoate 370, two patients became nauseated and one of them vomited about 45 s after the injection. Both of these patients experienced a decrease in BP and one had bradycardia (asystole) of 0.94 s. A fourth patient reacted with urticaria following the injection of metrizoate 370.

DISCUSSION

EEG At selective cerebral angiography in adults inconstant and irregular changes in EEG have been found using hyperosmolar ionic contrast media (7,25,34). The low osmolality compounds metrizamide, iohexol and ioxaglate induce few EEG changes following cerebral angiography (27,33,37).

Some investigators have questioned the sensitivity of EEG as a measurement of cerebral toxicity (16), as clinical investigations showed no alterations in EEG following selective cerebral angiography and angiocardigraphy (20,23,24) and earlier

rabbit experiments required very large doses of contrast media to produce EEG abnormalities. In our investigation we found changes in EEG in 65% of the patients. These changes in EEG were in all but one (metrizoate 280) brief and transient. The changes nevertheless indicate a toxic effect on the brain when the blood in the arteries supplying the brain is exchanged with more or less diluted contrast media which for a short time may influence the exchange of oxygen and glucose to the brain. We used continuous recording with 16 electrodes which may explain our detection of these brief EEG-changes.

Changes in heart rate

Bradycardia Three patients (metrizoate) became nauseated and vomited in connection with bradycardia and hypotension. Patients without bradycardia did not become nauseated or vomit. Only metrizoate 280 induced significant bradycardia. The mechanism behind this bradycardia is unclear.

Previous investigations on selective cerebral (13,21,26,28, 40), coronary (10,31,32,33), supraaortic or aortic root (8,12) injection have shown that bradycardia may be induced immediately or a few seconds after the start of injection. Bradycardia following aortic arch injection has previously been briefly reported in animal investigation without attempts to explain its cause (11,19).

By comparing the time of the commencement and the maximum of bradycardia with the time for maximum radiographic density in the different vessels (Fig. 1) the hypothesis is advanced that the bradycardia initially is elicited by a reflex in the aortic arch but may be superimposed by reflexes from the carotid or coronary territories.

Upon comparing the composition of the different contrast solutions, we consider that the bradycardia in our investigation (metrizoate 280) is induced by either the presence of meglumine and/or the absence of sodium and/or the relative lower viscosity but hardly the hyperosmolality of the contrast medium, as

metrizoate 280 induced more bradycardia than the more hyperosmolar metrizoate 370 (Table 1).

Tachycardia, blood pressure and subjective responses

Our results indicate that ioxaglate induces less changes than metrizoate in these three parameters, which reflect the influence of the hyperosmolality of the contrast media on the peripheral vascular system with vasodilatation and also reflect the wellknown correlation between the degree of osmolality and the degree of subjective responses as previously shown (2,3,9,29). The second peak in heart rate recorded after administering metrizoate 280 and 370, may be due to recirculation of the contrast media to the peripheral tissue.

Most patients referred for aortocervical angiography suffer from pronounced cardiovascular disease and have stenosis or occlusion of one or more of the arteries supplying the brain. We therefore consider it unfavourable to expose these patients to a fall in blood pressure such as that induced by metrizoate 370 in our investigation.

Image quality Detailed evaluation of the time of appearance and degree of filling of vessels during angiography is a difficult task and there are few reports in the literature (35). Some investigators have found a difference in image quality of the cerebral arteries between various ionic, monomeric contrast media, which they have ascribed to the difference in viscosity (5,15). In our investigation all factors that could influence image quality, except for the contrast media, were held constant between the different intraindividual injections. Two radiologists evaluated the image quality according to an arbitrary scoring system. The possibility to distinguish between small differences in image quality may be questioned. Every arbitrary system for evaluation image quality is based on a high degree of subjectivity. We were, however, able to register statistically significant differences between the different contrast solutions.

Ioxaglate 320 produced better image quality after subtraction

than the two 280 solutions. Metrizoate 370 was better than ioxaglate 320 on the original key angiograms. It is hypothesized that the increase in iodine concentration of 40 and 50 mg I/ml, respectively, partly accounts for the better image quality. It may also be due to the increased viscosity of the contrast solution and the increased effective viscosity inside the aortic arch immediately following the injection, as an increase in osmolality of a solution also affects the crenation of erythrocytes and thereby increases whole blood viscosity (6). The influence of high viscosity on image quality may be due to a less degree of turbulence, which is inversely correlated to the degree of viscosity (30). A high viscosity of the injected contrast solutions may then result in a more coherent bolus causing better radiographic density at the carotid bifurcation. As a result the flow will be low along the inside of the vessel resulting in a better demarcation.

After subtraction there was no significant difference in image quality between ioxaglate 320 and metrizoate 370. The increase of image quality due to the subtraction technique probably adds very little to the already high image quality on the original key angiogram induced by metrizoate 370.

Involuntary movements Few reports are found concerning motion artifacts induced by involuntary movements and their influence on the image quality, especially the subtraction procedure (14). In our investigation involuntary movements were frequent following injections of all contrast solutions with no difference between various solutions in the early phase of angiography (which corresponds to the time for the key angiogram). The motion artifacts that occurred late were less pronounced after ioxaglate than after metrizoate injection, reflecting the difference in osmolality between the contrast media and its influence on the subjective response. This indicates that the early movements may be induced by other factors than contrast media, such as the noise from the equipment. Improvements in this regard can probably be more easily achieved with silent equipment rather than by low osmolality of the contrast medium.

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